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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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JANUARY 1945

THE CHEMOTHERAPY OF SYPHILIS*

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SOME years ago I was so misguided as to have joined the long ranks of doctors who had written books on the treatment of syphilis. I was sufficiently bold, eleven years ago, as to entitle my own effort "*The Modern Treatment of Syphilis*" (the italics are new and ironical). To-day my own book and the many which preceded it are of historical interest only, and when now the question is asked "How do you treat syphilis?", my answer is "I don't know, but in company with many others, I'm trying to find out."

In an effort to clarify thinking, it has seemed profitable to review the chemotherapy of syphilis over a period of 451 years from the first appearance of the disease in Europe in 1493 until the present day, to be entirely accurate until eight o'clock on the evening of October 12, 1944. Such minute accuracy in point of time is not only desirable but actually necessary, since developments are now so rapid as to change the treatment of syphilis almost from hour to hour. A review of this type is of more than historical interest, since it involves consideration not only of what doctors have done and are now doing, but also of

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why and how these things have been and are being done. It is the "why and how" of the past and present that are important for the future.

Parenthetically, one might believe from the medical literature of the past few years that the very word "chemotherapy" dates from the introduction, only yesterday, of the sulfonamides. Actually, chemotherapy may be said to have begun more than 450 years ago with the disease under consideration tonight, syphilis.

The chemotherapy of syphilis is divisible into three time periods of very unequal length, the first lasting 410 years, from 1493 to 1903, the second of 40 years, from 1903 to 1943, the last, in which the doors of knowledge have as yet opened only a tiny crack for 16 months, from June, 1943, to the present moment. The amount of space devoted in this presentation to these three time periods must be in inverse proportion to the duration of each.

The first 410 years may be dismissed in a few words. When syphilis was first recognized as a new disease by our medical colleagues of the 15th century, its treatment, like the treatment of almost all other diseases, developed on a completely empirical basis. The entire gamut of the Renaissance pharmacopeia was tried, singly and in multiple combinations, ranging from blood letting to hen's dung. Of these, none was successful except mercury, which first came into general use about 1500. This poisonous metal did seem to be successful in healing the open lesions of the disease, though whether it was actually curative was the subject of a 400 year long medical debate, never finally settled until mercury had become obsolete. Given its demonstrated healing powers, however, various methods of its administration were elaborated, and unhappy patients were mercurialized by mouth, through the lungs by inhalation, through the skin byunction, and later parenterally by intramuscular or intravenous injection. Two facts became evident within a few years, that mercury in excess produced grave and even fatal toxic manifestations, and that to effect the apparent cure of syphilis in an important proportion of cases, it was essential to continue the use of mercury over a very long period, measured in terms of years.

These two facts produced two opposing schools of medical thought, important because of their bearing on subsequent developments. One group of physicians believed that mercury should be given in massive doses, to the point of producing serious toxic symptoms in the patient, from which he was permitted to recover by a rest period without treat-

ment One single course was demonstrably ineffective Therefore, many such courses should be given, and the intermittent treatment of syphilis was born Another group, convinced of the undesirability of adding the dangers of mercurial poisoning to the discomforts and hazards of syphilis, preferred to use less strenuous forms of treatment, with the drug given in small doses without the interruption of rest periods, the analogue of later continuous treatment

In complete ignorance of the cause of syphilis, of the biology of the disease in man, of immune processes, and of the mechanism of action of mercury, these two schools, one of intermittent and the other of continuous, but both prolonged, treatment systems, flourished side by side for four full centuries, during which the only minor advance was the introduction in the early 19th century of iodine This drug, given as a halogen iodide, was shown to have healing but definitely not curative effect in syphilis, presumably on the basis of its ability to "dissolve" granulomatous tissue It came to be used empirically in combination with mercury on the theory that by speeding up the healing of lesions, it enhanced the penetration of mercury into those lesions and thus aided in the destruction of the then unknown agent of the disease

In the seven-year period, 1903 to 1909, all this was changed In 1903, syphilis was for the first time transmitted to experimental animals by Merschnikoff and Roux, thus permitting the laboratory study of existing and new methods of treatment In 1905, the causative agent of syphilis, the *T pallidum*, was discovered by Schaudinn, thus allowing for a systematic study of the biology of syphilitic infection In 1907, the blood test for syphilis (now possessing so many modifications as best to be known by the generic term "serologic test for syphilis," abbreviated STS) was developed by Wassermann, Neisser and Bruck, thus immensely widening the opportunities for diagnosis, for immunologic study, and for evaluating the effects of treatment Finally, in 1909, the modern chemotherapy of syphilis was born through the discovery of salvarsan—606—by Ehrlich and Hata

The use of arsenic in the treatment of syphilis and the eventual discovery of 606, was no accident, but the result of carefully planned chemical and biologic experimentation over a period of years The popular name of the drug represents the fact, now often forgotten that it was the six hundred and sixth preparation which Ehrlich and his co-workers had developed On the basis of his experimental studies

Ehrlich originally hoped that syphilis could be "cured" with a single injection of the drug—"therapia magna sterilisans"—and indeed, this was and is possible in experimental animals

In man, however, and in doses capable of safe employment, the hope was not realized. Patients with early syphilis treated with a single dose of 606 relapsed in high proportions. To meet this disappointment, two expedients were promptly tried—first, to increase the individual dose past the margin of safety advised by Ehrlich, an attempt promptly abandoned not only because of risk to the patient but also because of therapeutic ineffectiveness, second, to give repeated injections of the drug, at first a few, and later as the inefficacy of this was demonstrated, many. The custom of spacing such injections at weekly intervals was based in part on convenience but more importantly on the rate of excretion of 606, which was completed within five to seven days, and in the effort to avoid cumulative toxic effects. Eventually, it was found, in early syphilis, that 606 alone, in any single amount or by repeated doses at any intervals, still provided a relatively high relapse rate, and the minds of clinicians reverted to the possibility of combining arsenic with mercury.

In the meantime, the experimental laboratory had demonstrated that arsenic, as exemplified by 606, was actually spirocheticidal, and that in experimental animals it was curative with a therapeutic ratio of approximately 10, i.e. the lethal dose (MLD) divided by the curative dose (MCD) equalled 10. At the same time, similar laboratory studies had shown that mercury was likewise spirocheticidal, but that its therapeutic ratio was approximately 1, i.e. the dose necessary to cure an infected animal about equalled the killing dose. The beneficial action of mercury in human syphilis, if any, remained and still remains without adequate explanation.

Nevertheless, and in the face of this discouraging experimental evidence concerning mercury, its clinical trial in combination with arsenic quickly demonstrated important advantages, in terms of lowered incidence of relapse and probable eventual cure, over the use of arsenic alone.

Now arose important considerations. Should these two drugs be used separately or simultaneously, continuously or intermittently, and for how long should treatment be continued? On these several points, there was no agreement because of still inadequate knowledge of the

biology of syphilitic infection, the toxicology of the drugs, or their exact mechanism of action. Looking back to the four centuries of experience with mercury, empirical systems of treatment were devised, one of which employed simultaneous courses of salvarsan and mercury separated by rest periods, the other giving courses of each in alternation, treatment being continuous.

Gradually and with increasing clinical and experimental evidence, it became clear that the continuous method of treatment possessed important theoretical and practical advantages. When the drugs were given together by the intermittent system, toxic symptoms from each were more frequent and more severe, the danger of producing a strain of organisms simultaneously drug resistant to both was ever present. The interpolation of rest periods to permit the recovery of the patient from the effects of treatment enhanced the possibility of relapse unless actual "cure" was accomplished by the first course of treatment. Given separately by the continuous system, all these hazards were avoided. The ultimate proof of the pudding lay in final clinical outcome, and by 1926 it had been established that for early syphilis, the continuous method of treatment produced results far superior to those attainable with any other method.

The difficulty lay in the length of time necessary to accomplish these results. Here, by a system of trial and error, and by comparative evaluation of relapse and "cure" in groups of patients given varying amounts of treatment, it was determined that with courses of arsenic injections given at weekly intervals, separated by courses of mercury, 12-18 months of treatment was necessary for early syphilis, 6-12 months for latent syphilis, and varying periods of time, all measured in years, for various types of late syphilis.

This unfortunate prolonged period of treatment, together with the disagreeable, expensive, and sometimes dangerous features of it, posed grave practical difficulties in the way of its mass application. Many patients were too stupid to complete the tedious grind, for all, it was too dangerous, too time-consuming, too expensive, and other expedients were constantly sought.

At first these took the form of attempts to develop arsenical drugs less complicated to administer and less dangerous than 606, which by now was known in this country as arsphenamine. From this search, there came neoarsphenamine, silver arsphenamine, and several others.

In 1925, bismuth was first introduced, and this drug, with a therapeutic index of about 3 to 5, as compared to 10 for arsphenamine and 1 for mercury, gradually came to replace the latter. Still, however, the system of prolonged continuous treatment persisted with alternating courses of some arsenical drug and bismuth (the latter replacing mercury and improving upon its results).

In 1933-1934, two new developments occurred. Tatum and Cooper restudied and re-introduced into the treatment of syphilis an arsenoxide. This substance, the therapeutically active eventual oxidation product of all arsphenamines, had originally been studied but abandoned by Ehrlich as too toxic for human use. In therapeutically effective doses in man and animal, however, it developed that this drug (marketed in this country under the trade names of mapharsen, clorarsen, or phenarsine hydrochloride) was actually less toxic than its parent arsphenamines, that it was excreted from the body with much greater rapidity (from 2 days instead of 5 to 7), and that it was as therapeutically effective as the best of the arsphenamines, 606 itself. Combined with these advantages was simplicity of administration.

Likewise in 1933, Chargin, Leifer, and Hyman in this country and Tzanck in France commenced a re-exploration of the effect of massive doses of arsenic given in a short period of time. Undismayed by the failure of earlier trials of various intensive treatment systems and without preliminary laboratory study, they treated a series of patients with 4-5 grams of neoarsphenamine given by continuous intravenous drip over a five-day period.

Later, because of deaths and a high incidence of serious reactions in the nervous system, mapharsen was substituted for neoarsphenamine, with equally satisfactory clinical results and with a reduction in the incidence of toxic reactions, but still, however, with the frequent occurrence of serious toxic encephalopathies and a mortality rate of approximately 1 to 200 patients treated.

The results obtainable by this intensive method of arsenotherapy given within a five-day period, were equally as good as or better than the best obtainable with prolonged treatment systems requiring 12-18 months for completion, and the method had the inestimable advantage that almost all patients actually completed treatment, although at a considerably increased risk.

This radical innovation quite properly promoted a systematic re-

investigation of the whole problem of metal chemotherapy of syphilis, a laboratory study which should have been carried out many years earlier. Careful experimental study in animals by Eagle and Hogan revealed that the curative dose of mapharsen in early syphilis in rabbits was remarkably constant (5-7 mg/kg of body weight) regardless of the time interval over which the total dose was given, but that the toxicity of the drug varied in direct relationship to the duration of treatment. Administration by continuous intravenous drip carried no advantage but some actual disadvantages over multiple intravenous injections. Further, the results of mapharsen therapy in animals were improved by the simultaneous administration of bismuth, without significant increase in the toxicity of either drug. Finally, it was shown that the curative dose of mapharsen in early syphilis in man was 3-5 times the curative dose in the rabbit (i.e., 20-35 mg/kg), and that the same considerations as to toxicity applied in man as in the animal.

This relation of curative to toxic dose permitted the statement that as to arsenic-bismuth chemotherapy of early syphilis, there is no single optimum treatment scheme. Given a required total dose of 20-35 mg/kg of mapharsen (1200-2100 mg) administered either by intravenous drip or multiple individual injections, various treatment schemes may be devised with expected and actual mortality rates determined by the duration of treatment. Thus, with all treatment schemes compressed within ten days or less, the mortality is about 1/200. With schemes prolonged for ten to twelve weeks, the mortality from treatment falls to 1/3000 or less. Within these extremes of ten days to twelve weeks, essentially the same clinical results may be achieved, with mortality rates selected as desired to meet the exigencies of the particular patient or the local situation.

Meanwhile, in parallel with these studies of intensive chemotherapy and indeed antedating them, were progressing other studies of the effect of so-called non-specific methods of treatment, especially fever. The clinical acumen of both medieval and modern physicians is challenged by their failure to appreciate the significance of the first record, in the *Autobiography of Benvenuto Cellini*, of the "cure" of his own syphilitic infection by the fever of intercurrent malaria. Not until 1917 did the classical clinical studies of Wagner von Jauregg establish the value of fever (malaria) in the treatment of that most serious manifestation of syphilis, general paresis, further clinical and experimental in-

vestigations have thoroughly established the value of fever therapy, whether from induced malaria or by mechanical means, in almost all forms of neurosyphilis. Indeed, in patients with neurologic damage from syphilis, fever alone is more efficacious than any form of chemotherapy, and there is reason to believe that post-fever chemotherapy does not add much to the results obtained from fever alone. Curiously enough, however, and for reasons not yet clearly known, the value of fever therapy per se is almost entirely limited to neurosyphilis. There is ample clinical and experimental evidence to show that fever alone, in any degree tolerable by man, will not cure early syphilis. However, more or less empirically, there have been numerous clinical attempts, in all stages of syphilis in man, to combine fever therapy with chemotherapy, resulting, in early syphilis, in an effort to compress all treatment into a single day (the highly publicized "one-day cure of syphilis"). The laboratory has again lagged behind the clinic in the study of this important problem, but forced into it by clinical pressure, the experimentalists have now demonstrated (for phenarsine hydrochloride in syphilis) that while the toxicity of the drug is doubled at fever temperatures, its therapeutic efficacy is increased four-fold or better. These toxicity/efficiency ratios during fever appear also to hold for many other drugs, e.g., the sulfonamides.

With any method of use of the arsenic-heavy metal treatment of early syphilis, whether in 12 to 18 months of continuous weekly treatment, in 5 days to twelve weeks of intensive or semi-intensive treatment, or in 1 to 3 days of combined fever-chemotherapy, the results are about the same. These are 80-85 per cent "cure," as measured by prolonged seronegativity of blood and spinal fluid and freedom from early relapse. The late results of adequate prolonged therapy are also known, and comprise about 5 per cent of the development of cardiovascular and neurosyphilis in contrast to the 30-40 per cent expected in the absence of all treatment. With the newer intensive and semi-intensive methods, these late results will not be available for another generation.

The applicability of the prolonged arsenic-heavy metal systems to the treatment of various types of late syphilis has been fairly well determined after a total period of thirty-five years, as has that of fever therapy, alone or combined with chemotherapy, to neurosyphilis. As to the newer intensive treatment systems, nothing is as yet known in this respect.

Through all the years 1493 to 1943, 450 of them, the questions uppermost in the minds of doctors have been, both in respect first to mercury, later to arsenic-heavy metals, what preparations to give? by what route of administration? alone or in combination with another drug or non-specific method of treatment? continuously or in alternation? and for how long? In their simplest form all these questions look toward the solution of a problem inherent in all forms of chemotherapy—whether of syphilis or some other disease—the time-dose relationship.

Through all these 450 years moreover attempts to solve these problems have proceeded (until quite recently) on an individual rather than on an organized basis. In all countries (until recently) laboratories have thought it sufficient to announce that a given drug or a particular preparation of it was of value in syphilis. How the drug should be used in terms of the above questions was in general left to the clinicians. The latter working independently of other clinicians and therefore necessarily each on a small scale tried various systems and combinations of treatment each trying to persuade the other that his particular plan was best. For the first time, in the late 1920's, the League of Nations and a little later the Cooperative Clinical Group (sponsored by the U. S. Public Health Service) undertook a systematic study of the results of various treatment schemes in early syphilis. The result of this world-wide disorganized study was that as late as June, 1943—only a short 17 months ago—there was still disagreement among doctors as to the best manner of treating even the simplest form of syphilitic infection, the acute early stages of the disease.

Within almost the twinkling of an eye, this picture was even more abruptly changed, in June 1943, than by the advent of salvarsin, 34 years before. In that month, Mahoney, Arnold and Harris demonstrated that penicillin was effective in early syphilis in rabbit and man. This drug, for all practical purposes completely non-toxic, appeared to be curative in early syphilis when administered within the brief period of eight days. There was initial promise that a rapid cure of early syphilis had been discovered which was completely safe—lacking all the hazards of the poisons arsenic and bismuth.

Fortunately for penicillin and the advancement of knowledge concerning it, our country was at the moment and still is engaged in a great war. The problem of syphilis, especially early syphilis, is of paramount importance to the Armed Forces, and for the sake of conserving

man power, it is urgent to determine quickly the optimum method of use of this new and revolutionary drug. In place, therefore, of releasing penicillin to all of the syphilis clinics of the country, each of which might pursue its own independent avenues of study, it was clearly obvious that an organized investigation was essential.

This was brought about through the cooperation of the U S Army, Navy, and Public Health Service and the Committee on Medical Research of the Office of Scientific Research and Development, under the general auspices of a Penicillin Panel appointed by the Subcommittee on Venereal Diseases, National Research Council. Together with the Army, Navy, and the Public Health Service, some twenty-five civilian clinics were invited to participate in a study of the effect of penicillin in early and late syphilis, the results in early syphilis to be pooled and statistically analyzed as a group.

In addition, the cooperation of four laboratories was enlisted in order to study in experimentally infected animals the various permutations of the time-dose relationship in both early and late syphilis, such other important issues as the effect of penicillin in combination with other chemotherapeutic agents as arsenic and bismuth, or in combination with fever. Both in clinic and laboratory are progressing comparative studies of the several penicillin salts, sodium, calcium, and ammonium, methods of prolonging the action of the drug, and other important pharmacologic investigations.

The urgency of the military situation does not permit, however, that the application of penicillin to the treatment of syphilis in human beings be postponed until all available information can be had from experimental animals. Experimental study must progress simultaneously in man, and is rendered particularly feasible because of the almost complete lack of toxic effects from the use of this drug.

The problems of special importance to the Armed Forces are early, latent, and neurosyphilis, in that order. Most of the clinical emphasis has thus far been placed on the two of these in which results are readily measurable, early and neurosyphilis. The problem of latent syphilis has been relegated to the future for large scale study, primarily because it is essentially a long term investigation, the results of which depend on ultimate clinical outcome after many years of observation.

In early syphilis, all cooperating clinics have agreed to work on assigned treatment schedules devised to investigate the effect of the

several variables of (1) route of administration, (2) the interval between injections, (3) the total duration of treatment, and (4) the total dose of drug. Early effort has been centered on these four factors, in order to determine as rapidly as possible the effect of penicillin alone. The fifth variable—the effect of penicillin in combination with other agents (e.g., arsenic bismuth, fever)—has as yet barely been touched clinically, though it is of course under laboratory study.

The results to date permit a number of general statements. A single injection of penicillin, by any route of administration and in whatever amount, is practically ineffective in early syphilis of man or animal; multiple injections are necessary. The intramuscular route of administration of aqueous or saline solutions of penicillin is certainly as good as and probably superior to the technically more difficult intravenous route, whether the latter is given by repeated injections or by continuous drip. With aqueous or saline solutions the optimum interval between single intramuscular injections ranges from three to six hours, certainly not in excess of the latter. Absorption and excretion of the drug is complete within this time range; methods of prolonging absorption by means of such expedients as oil suspension, implantation of pellets, etc., are not ready for mass experimental study in man. The intrathecal injection of penicillin in patients with early neurosyphilis (e.g., asymptomatic neurosyphilis, acute syphilitic meningitis) is not necessary, although the drug does not penetrate into the cerebrospinal fluid; it does penetrate the diseased tissues of the nervous system. This is almost certainly true also in late neurosyphilis.

With these data in hand, treatment schemes so far employed have been built around the factors of repeated intramuscular injections of aqueous or saline solutions of penicillin given at intervals of every three to six hours day and night. The next problem has been to determine total dose and total duration of treatment within the perennal time-dose relationship.

In man, the first effort in this direction was to study the comparative effectiveness of four treatment groups, given total doses of penicillin within the 20-fold range of 60,000 to 1,200,000 units divided in 60 intramuscular injections given every three hours day and night for a standard duration of 7¹/₂ days. At once, there emerged the fact that within this enormous variation of dose, immediate results were practically identical. Spirochetes disappeared from open lesions within the

time range of six to sixty hours (average about twelve hours), lesions healed with great rapidity, and there was a rapid trend toward reversal of the blood serologic test which proceeded at almost the same rate regardless of dosage. These factors could not be used, therefore, to determine the effectiveness of a given treatment schedule. The only factor which has so far proved of importance is the comparative incidence of relapse, clinical or serologic, and determination of this relapse rate is possible only after the passage of many months of time. It must be repeatedly emphasized, therefore, that the data so far available are based on relatively few cases followed for relatively short time periods. Several thousand patients have been treated, but only a few hundred of them have been followed for six months or longer.

Keeping in mind the preliminary nature of the results, however, it is already indicated that within the range so far studied the relapse rate is in inverse ratio to total dosage, the lower the dose, the higher the relapse rate. With a total dose of 60,000 units given in $7\frac{1}{2}$ days, the indicated eventual early relapse rate is 100 per cent, with 300,000 units, about 75 per cent, with 600,000 units, about 40 per cent, and with 1,200,000 units, about 15-20 per cent. This last rate, 15-20 per cent, is only a little worse than the best that one can accomplish with arsenic-bismuth chemotherapy whether given by intensive, semi-intensive, or prolonged systems, and penicillin holds the inestimable advantage of freedom from all the serious risks of metal chemotherapy.

The next problem is, of course, the effect of much larger doses. Acting on the time-honored lay theory that if one pill is beneficial, two must be better, and four perhaps better still, a large series of cases has been treated with 2,400,000 units in $7\frac{1}{2}$ days, and is now under observation. The time elapsed is too short to permit definitive comparisons, but relapses seem less frequent than with half this dose.

Under simultaneous study is the variable of time. So far, only one comparison is possible. Given in 30 injections in 4 days, a total dose ranging from 600,000 to 2,400,000 units is perhaps less effective than when a similar dose is given in 60 injections in $7\frac{1}{2}$ days. Halving the duration of treatment is therefore not helpful, whether doubling it to e.g. 15 days, while holding the total dose constant improves the situation, is a problem for future study.

Also under current investigation is the effect of lengthening the interval between injections. Here it has already been established that an

interval of 12 hours is unsatisfactory, whether there is any material difference between 3 and 6 hour intervals has not yet been determined

Finally, in early syphilis, some animal studies and two small pilot groups of patients suggest that penicillin in combination with an arsenoxide (the latter given in eight divided daily injections totalling 5-6 mg/kg of body weight within 8 days) may be more effective than either drug alone

The treatment plans so far utilized by the cooperating clinics in early syphilis are shortly to undergo complete revision in order to provide further information as to the several variables involved. It is believed that with this type of organized investigation, optimum methods of use of penicillin in early syphilis can be developed within three to five years, thus obviating the thirty-five years of uncertainty which followed the introduction of arsenic

So much for uncomplicated early syphilis. Simultaneously, it has been shown that penicillin is apparently completely effective in early syphilis treatment-resistant to arsenic and bismuth, it appears to be of great value in the prevention of congenital syphilis in infants born of recently infected mothers, it produces dramatically favorable effects in early neurosyphilis, asymptomatic or meningeal, in both of which spinal fluid abnormalities improve with even greater rapidity than does the blood serologic test, and it is equally as useful in infantile congenital syphilis as in the acquired disease. (In infants, the total dosage employed in 8-12 days of time has ranged from 20,000 to 60,000 units/kg of body weight)

Patients who have relapsed, clinically or serologically, after any dose of penicillin have been re-treated with doses at present regarded as large (i.e., 1,200,000 to 4,000,000 units). So far, no example of penicillin resistance has been encountered, in the sense that relapsing lesions have responded as promptly as did the initial outbreak. It is probable that the relapse rate in re-treated patients will be higher, however, than in patients treated for the original attack, a phenomenon also obvious with metal chemotherapy

Late syphilis of various types presents a much more complex problem. Here the initial demonstration was that penicillin heals visible gummatous lesions of the skin and mucosae with even greater rapidity than does metal chemotherapy. In interstitial keratitis of congenital syphilis, the results are less spectacular, about 50 per cent of the pa-

tients treated have improved. In neurosyphilis of various types, ranging from asymptomatic neurosyphilis of mild degree to general paresis, little can as yet be said. Some degree of immediate clinical improvement is apparent in most symptomatic cases, but whether these results are as frequent or as complete as after fever therapy is as yet debatable. In most patients with neurosyphilis of any type, there is prompt improvement in the spinal fluid abnormalities, especially in cell count and protein content, and sometimes in complement fixation and colloidal tests as well. It is not yet known whether this clinical and serologic improvement will be maintained.

Dosage schedules in late syphilis are much more difficult to determine than in early syphilis, and many variables have been employed. In general, the major effort of study has been in neurosyphilis, and here, at the moment, four schedules are under trial. These are

- 1 Repeated courses of relatively small doses, e g, 1,000,000 units, separated by rest intervals

- 2 Single massive dose courses, ranging from 2,000,000 to 6,000,000 units, given within 8 to 20 or more days. In general, the larger doses are under study in patients with paresis, pre-paresis, or primary optic atrophy, the smaller doses in less serious forms of neurosyphilis.

- 3 Malaria plus 2,000,000-4,000,000 units of penicillin simultaneously administered, an expedient possible because of the lack of effect of penicillin on malaria. There is some indication that penicillin, like other drugs, is more effective at fever than at normal body temperatures.

- 4 Malaria followed by penicillin.

The evaluation of penicillin in late syphilis, and optimum methods of its employment, are obviously complicated problems which will require many years of study. Here, as in early syphilis, however, results will be much more quickly available through organized cooperation of many investigators than by isolated individual effort.

One further fact emerges from the use of penicillin in late syphilis of all types. There is evident a trend toward seroreversal of the blood test in a higher proportion of cases than was previously possible from metal chemotherapy. Whether this is necessarily a favorable sign would lead us into a discussion of the phenomenon of seroresistance, for which there is neither time nor space available here.

Reactions from penicillin are negligible except for the Jarisch-Herx-

heimer reaction, consisting usually of fever, sometimes of exacerbation of lesions, within the first twenty-four hours of treatment. The frequency and intensity of this reaction is related to dosage. It occurs in about 75 per cent of patients with early syphilis and about 30 per cent of those with latent and late forms of the disease.

The rapid and safe cure of early syphilis is just around the corner. It is desirable to note, however, that a method of treatment requiring a minimum of ten days of hospitalization for early syphilis is not practical for nation-wide application, especially in rural areas. It is not so much a question of more hospital beds (though this is important) as of the general problem of the economics of antisyphilitic treatment. A method of use of penicillin in ambulatory patients is essential, and is not yet in sight.

As matters stand at present, penicillin is a new and powerful addition to syphilotherapy. How best to use it, alone or in combination with other forms of treatment, is as yet undetermined but is under organized, nation-wide, governmentally sponsored study, from which definitive results may be expected rapidly to emerge. The desirability of continuation of such a scientific approach is exemplified by the historical background of the past 450 years, which I have so briefly reviewed tonight. Perhaps soon again, an answer can be given to the questions of doctor and patient: "How do you treat syphilis?"

THE CHEMOTHERAPY OF GONORRHEA *

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THE history of the treatment of the disease, gonorrhea, is as varied and as bizarre as any in medicine. The story spans a period extending from the time of the migration of the tribes of Israel to the immediate present. An almost incredible list of drugs and chemicals has been employed, as well as a variety of biologic preparations, serums, vaccines and filtrates. Their lack of effectiveness in combating the infection may best be attested by the difficulties and problems which were presented by the patient with gonorrhea up to the very recent past. The most remarkable chapters have been written within the last decade during which time the disease has passed from the domain of the local therapist and into the scope of chemotherapy.

In attempting an evaluation of the effectiveness of chemotherapy in gonorrhea, recourse will be taken to the appraisal of the two objectives of such therapy, namely, the curative and the public health or preventive. The former is based upon the facility and completeness with which the disease is brought to arrest and the individual returned to a state of health. The second appraisal takes into consideration the ability of the therapy to reduce mathematically the opportunity for transmission of the infection, thus becoming an instrument in the reduction of the incidence of the disease in a population group.

Not any attempt will be made to review or to comment upon the relative value of the many forms of treatment which have been advocated other than the following generalization. The drugs and chemicals whose effectiveness was dependent upon systemic response, and this may well include the biologic preparations, in a large measure failed to produce consistent curative results. Principal reliance finally centered upon the local application of various antiseptic agents. In the light of the histopathology of the disease, especially as concerns the male ure-

* Presented October 12, 1944 by Dr J F Mahoney at the Seventeenth Graduate Fortnight of The New York Academy of Medicine

thra, the possibility of even a most active germicide penetrating to the site of the inflammation without affecting adversely the tissue structure, appears to be remote. The duration of the disease and occurrence of complications in many instances reflected an unwise degree of vigor and heroism displayed in the application of local measures. On the whole, the entire concept of local therapy appears, in retrospect, to have been of limited curative value.

The sulfonamide era may be assumed to have had its inception in 1936 when the first of the sulfonamides, sulfanilamide, was made available for study. In the following year the publication of the results of a group of well-conducted studies established beyond a reasonable doubt that the compound was effective in the cure of gonorrhea through systemic or chemotherapeutic action. This conclusion was the first of a series of events, the cumulative effect of which has resulted in an almost complete alteration in the potentialities of the disease as regards its ability to injure the human. The finding also ushered in one of the most dramatic chapters in medicine.

The shortcomings of sulfanilamide therapy were soon apparent. An objectional, but not significant or dangerous, cyanosis accompanied the ingestion of curative amounts of the compound. When used over a prolonged period, or in excessive amounts, definite damage to the blood-forming organs was a possibility. A degree of mental confusion and some interference with muscular coordination rendered the therapy somewhat dangerous for other than hospitalized patients. Of primary importance from the public health standpoint was a tendency to produce symptomless states in which virulent organisms still persisted, thus giving rise to a carrier problem. Although by far the most efficient remedy in gonorrhea which had been produced, the drug rapidly lost favor and ceased to be a factor with the coming of the more adaptable and more effective sulfonamides.

Sulfapyridine was the second of the group to attain usefulness in the therapy of gonorrhea. It was proven to be capable of producing a high cure rate. Its action was prompt and clearcut. However, the use of the drug was accompanied by a disagreeable gastrointestinal toxicity which also restricted its use to patients under close supervision. This compound, too, rapidly passed from favor when the most important member of the group, sulfathiazole, was developed. This last drug displayed a remarkable freedom from the production of toxic reactions.

when used in a conservative manner and was credited with producing a cure rate approximating 85 per cent under favorable conditions. Sulfathiazole has been generally used by clinicians, and almost exclusively by health organizations, in the management of the disease and was not replaced in popularity by sulfadiazine or others of the more recent sulfonamides.

In an excellent review Henry¹ summarizes current thought on the subject of the mode of action of the sulfonamides. There is general agreement that the present concepts undoubtedly will change as more complete knowledge becomes available. The consensus at the moment favors the view that this group of compounds inhibits the growth of cells and that this inhibition involves not only the bacterial cell but the tissue cells as well. The degree of inhibition seems to be dependent upon the concentration of the compound, the type and the environment of the cell.

Evidence available at this time supports the view that the bacteriostatic effect of the compounds is due to a direct inhibitory influence upon one or more enzymes. That the action is reversible may be demonstrated by the restoration of cellular activity after washing out of the sulfonamide compound.

One group of investigators believes that the sulfonamides interfere with the enzymes which catalyze anabolic and catabolic reactions within the cells. The antagonism of para-aminobenzoic acid to the action of a sulfonamide is explained on the assumption that an excess of para-aminobenzoic acid effectively minimizes the combination of the sulfonamides with the enzymes necessary in anabolic reactions which utilize para-aminobenzoic acid as a substrate. However, there appears to be support for the belief that the sulfonamides produce primary inhibition of one or more enzymes concerned with oxidation-reduction and thus interfere with cellular division.

Dorfman, et al.,² point out that the bacteriostatic effect of sulfapyridine and sulfathiazole appears to be caused by the inhibition of reactions other than those which are influenced by sulfanilamide. They conclude that the action of the sulfonamides may be explained on the basis of differential interference among several enzyme reactions. Such a selective capability appears to be indicated by clinical experience.

Early experience with sulfonamide therapy in gonorrhea demonstrated that a proportion of patients, approximating 15 per cent with

sulfathiazole, failed to attain curative response following a routine of treatment which proved to be effective in a large majority of instances. The reasons usually put forth to explain these failures were (a) the chance encountering of a strain of *N* gonorrhoeae whose biology differed from the average to the extent of being resistant naturally to chemotherapy and (b) that the failure patients represented a deficiency, or absence, of some host factor which was essential to the effective action of the compound. A brief discussion of these concepts may be of interest.

At the outset of the work it was necessary to ascribe any resistant characteristics to natural phenomena, as not any of the strains had been exposed previously to the sulfonamides with sufficient frequency to stimulate a biologic change of the degree manifested by the resistant strains. Hence, it must be assumed that the ability to survive was the result of experience with destructive agents other than the sulfonamide type of compounds. Just why only a relatively few strains should have had this experience is not clear.

It was not until recently that a specific contribution to the subject of strain resistance could be made. In utilizing this reference and material, recourse will be taken to an unpublished study, the results of which probably will be made available in the near future.

Under conditions of incarceration male volunteers were exposed to infection through the urethral instillation of culture material containing virulent gonococci. The percentage capabilities of various strains to produce clinical disease does not enter into present considerations. Of interest is the evidence which points to the presence of strain resistance and to the tendency of an individual strain to follow a characteristic behavior pattern as regards its response to sulfonamide therapy.

A strain of *N* gonorrhoeae isolated from a prostitute who had failed to attain clinical cure through repeated courses of sulfonamide therapy was purified and utilized as inoculum in the exposure of a group of 19 volunteers. Of this group 10 developed clinical gonorrhea confirmed by laboratory findings. All of the patients failed to respond to sulfathiazole therapy in a satisfactory manner and were brought eventually to clinical and bacteriological cure through the use of penicillin.

The converse of this was also studied. A strain of *N* gonorrhoeae isolated from a male patient who had responded in a satisfactory man-

ner to sulfathiazole therapy produced clinical disease in 25 volunteers. All of this group attained prompt relief of symptoms and negative bacteriological findings following the use of sulfathiazole.

Although the material is not large the observations were very precise and pointed toward the ability of strains to retain susceptible and resistant characteristics through the small number of passages observed.

The second concept, that involving host factors, may be dismissed rather hurriedly because of the lack of exact information upon the subject. Early in his studies in chemotherapy Ehrlich postulated that a degree of immunological response was a prerequisite to the efficient action of any chemotherapeutic compound. This thesis must have been based upon philosophic grounds as the procedures which are used to measure the usual immunological responses fail to show any difference in the economy of patients whose infections responded to the sulfonamides and those which failed. Neither are clinical means available which serve to identify or measure the host factors which serve to enhance the action of the chemotherapeutic agent.

That host factors are of importance is demonstrated by the results which are obtained in patients who contract the disease from a single source and hence should be considered as having been infected by the same strain. In several instances of record, one patient has been known to attain a prompt cure while the second has proven resistant to sulfonamide treatment. The identification of these host factors and their stimulation or alteration to assist better in the promotion of drug action still constitutes one of the most important problems in chemotherapy.

In attempting an estimate of the over-all benefit which has been derived from sulfonamide therapy the published cure rates probably present a conflicting picture. In studies carried out under hospitalized conditions wherein the patient actually receives a stipulated amount of the drug over the stated period of time and where the post-treatment observation is carried out in a precise manner and the patient is maintained free from a reasonable possibility of reinfection, the cure rates have approximated 80 per cent. In studies in which outpatient material was employed lower rates have, as a rule, been produced. This decline in effectiveness is to be expected as the actual carrying out of the outpatient treatment schedules depends entirely upon the type of cooperation which the patient contributes. Basing conclusions upon the findings

of studies wherein the most essential factor, that of total ingestion of drug, is at the discretion of the patient will always be hazardous

Because of the lack of an accurate statistical backlog it becomes impossible to follow the trends of gonorrhea in anything like a precise manner. The peace time levels are not known and probably will not be known in the future. Reflected in the statistical patterns, however, are evidences of marked increases in prevalence during and following periods of national conflict. The upstrokes due to World War I are clearly defined. At the present the gonorrhea situation appears to be entirely favorable. The anticipated increases in rates have not, up to this time, taken place. Such reports as are available from military organizations located within the continental limits of the United States are appreciably below those of the previous conflict. These rates are generally in the neighborhood of 30 per 1000 per year for the venereal group of diseases with gonorrhea contributing the usual two-thirds.

Any decline in the gonorrhea rate, if it be the result of a man-made effort and not a natural cycle in the disease itself, must be ascribed to the efforts which have been directed toward the control of the disease in recent years and which have been augmented greatly during the war period. Basically, these efforts have been dependent completely upon sulfonamide therapy until quite recently when penicillin has been added. The ability of the therapy to curtail the period of infectiousness, thereby markedly reducing the mathematical opportunity for transmission in a fair proportion of patients, may be responsible for placing in motion a geometrically progressive decline in incidence. Such a decline may be expected to continue unless some unforeseen and unsuspected factors arise to impede the working of an accepted law of epidemiology.

Before a true estimate of the real value of sulfonamide therapy could have been established the antibiotic substance, penicillin, was found to possess an almost miraculous efficacy in checking gonococcal infections.

The developmental work in penicillin therapy was carried out largely on the initiation of the National Research Council. The early studies rapidly demonstrated the effectiveness of the product and subsequent efforts were directed toward the finding of the optimal dose-time ratio.

In one of the early studies³ a treatment period of 48 hours was

employed Because of the frequency of dosage and the use of intramuscular injections hospitalization of the patients became necessary The opposite extreme was reached in a very recent study in which Van Slyke⁴ and others utilized treatment periods of 4 and 8 hours, respectively, giving only two injections, each of 80,000 units of penicillin The cure rates attainable with this routine were high—92 per cent and 96 per cent The inference is inescapable that a routine of this kind employed in clinics or in office practice would become a most effective instrument in a mass attack upon the disease

In the matter of dosage, a wide range of effectiveness is probably demonstrable in different individuals Excellent results have been observed in patients receiving as low as 50,000 units and failures at 200,000 units This, again, may be an expression of the presence or absence of host factors A safe and efficient level of treatment appears to involve, roughly, a total of 120,000 units given by intramuscular injection, 20,000 units at 3 hour intervals over a treatment period of 15 hours The amount of drug may be doubled or the duration of treatment reduced appreciably without greatly altering the cure rate

In a recent article, Sternberg and Turner⁵ report upon Army material The work is important because the generally satisfactory results produced represent the pooled experiences of a group of clinicians rather than those of an individual, and also because of the fact that it was not necessary to take recourse to any type of therapy other than penicillin to effect a cure in approximately 1800 patients included in the study A similar experience has been reported by others

Not anything is known of the biologic mechanisms, or the reasons therefor, which produced in one of many species of mold the capacity for the destruction of bacterial forms of life, among them, the gonococcus The chemical nature of the substance is unknown or unrevealed Its mode of action, like that of the sulfonamides, is ascribed to the power of blocking enzymatic action which is essential to the economy of the bacterial cell In contradistinction to the sulfonamides is the fact that normal tissue cells are not involved in the action The real importance of penicillin lies not so much in its ability to destroy certain pathogens but rather to the impetus which its use has given to investigative work in the field of antibiotics The concept that antibiotics may be effective chemotherapeutic agents is itself old Dubos,⁶ in the development of gramicidin, made a most important contribution

Research of the future will be directed toward the discovery of other forms of life which possess the capacity to produce substances which may be utilized in the destruction of pathogenic organisms

In the recent literature⁷ some alarm has been expressed as to the role which will be assumed by gonorrhea in the future. The prognostications include the production of symptomless carrier states and of drug resistant strains which will move unchecked through a population group in the proportion of an epidemic. In this light, the sulfonamide compounds will come to be looked upon as harbingers of evil and precursors of calamity to be censured and condemned for promoting a relatively innocuous disease to a position of direful proportions.

In the experimental study previously referred to a total of 82 infections was produced and treated with penicillin and/or sulfathiazole. All were closely followed through prolonged post-treatment periods with careful clinical and cultural observations. Not any of this group was found to harbor the *N. gonorrhoeae* beyond the eighth (8) day after the cessation of clinical symptoms. This evidence, for what it may be worth, points away from any alarming tendencies toward the widespread development of carriers and the lack of faith in the completeness of cure.

Conversely, if these therapies continue to curtail the duration of the infectious period of the disease in a large proportion of instances, then surely the exponent of public health may look forward with confidence to a future world relatively free from the not entirely pleasant influence of gonorrhea.

It would be wrong to suggest that eradication might be well within the range of possibility, as the complete destruction of any species in nature runs counter to all biologic law. In all probability, the disease will always be with the human race but its capacity as a producer of human distress and suffering may be reduced to a minimum through the wise application of the knowledge which is available at the moment.

CONCLUSION

By way of conclusion, if the incidence of the disease as estimated at the present can be induced to remain at its present level for the duration of the war, an appreciable reduction may be anticipated when those at present living under military conditions again assume a more rational mode of existence. When to this influence upon the side of

the defense is added the most dramatic therapeutic agent ever placed at the disposal of the medical profession, with its recognized ability to curtail the infectious period to a matter of hours, then surely the incidence of this disease must further decline to a point where, everything else being equal, the disease should not be an important source of ill health to the human race and its position as a public health problem should have largely passed to a more worthy candidate

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THE MODE OF ACTION OF
CHEMOTHERAPEUTIC AGENTS*

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THERE are, theoretically, several independent avenues of approach to the problem of the chemotherapy of infectious diseases. One may conceive, for example, of the existence of chemical substances endowed with such physiological activity that they hasten recovery by stimulating the normal defense mechanisms of the body. There may be, on the other hand, other types of chemical agents capable of exerting a beneficial effect on the course of the disease by decreasing its toxic manifestations, either by combining with and neutralizing the toxic constituents and products of the parasite, or by rendering the host cells resistant to these poisons. In practice, however, the only significant results of chemotherapy to date have been obtained with substances which are capable of killing, or of inhibiting the growth of, the infectious agent in the invaded tissues of the host. The present discussion will be limited to an analysis of the mechanisms by which antiseptics and chemotherapeutic agents interfere with the living processes of bacterial cells.

The Receptor Theory The first step in the action of many if not all antimicrobial agents is the fixation of the agent upon some constituent of the susceptible cell. This hypothesis was first clearly formulated by Paul Ehrlich, who believed that antiseptics and chemotherapeutic agents exert their action by combining with certain chemically reactive groups of the cell. He called these hypothetical cellular structures "receptors." Differential susceptibilities to the different growth inhibitors could thus be explained by postulating the existence in the susceptible cell of a sufficient variety of receptors concerned in essential metabolic functions.

For a long time, the inadequacy of the biochemical knowledge concerning cellular structure and metabolism prevented any definition of the nature of the receptors in accurate chemical terms. Ehrlich him-

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self, however, had suggested that the arsenicals owe their physiological activity to their affinity for reduced thiol groups. Evidence has continued to accumulate that the cellular-SH groups are indeed the "receptors" which fix the arsenicals upon the susceptible organisms, and furthermore, it is also believed that the antimicrobial activity of the mercurials is due in part at least to the same type of chemical activity.

Further progress in the formulation of the receptor theory came from the analysis of the mode of action of the antibacterial dyes. Thus, the basic dyes (tryphenylmethane and acridine compounds in particular) appear to owe their biological activity to their basic ions, which form feebly-ionized compounds with the acidic groups of bacteria. Conversely, the acidic ions of the acid dyes (e.g., acid fuchsin) are assumed to react with the basic groups of bacteria giving rise to an ordinary type of double decomposition.

The same general type of acid-base reactions appear to constitute one of the primary steps in the action of other kinds of acidic and basic antiseptics, such as the synthetic soaps known under the name of anionic and cationic detergents. Although it is certain that these surface active compounds owe much of their bactericidal power to their physical properties, it is likely that they first unite with the bacterial cell through their acidic and basic groups respectively. It is worth mentioning at this time that the phenolic compounds have also been claimed to owe their antibacterial activity to a reaction between their acidic hydroxyl groups and some basic cellular components. Since reactions which occur slowly in the bulk phase may occur rapidly when the reactants are oriented in a surface layer, and since phenolic compounds are surface active and therefore orient themselves at the cell surface, the reactivity of the phenolic hydroxy groups can become very great in biological reactions. Even in the test tube, phenols can precipitate amines provided one reactant is of sufficient molecular weight or carries a lipophilic constituent. It is not unlikely, therefore, that phenols combine with the amino groups of bacteria. On this basis, phenolic compounds should be considered as anionic (acidic) antiseptics, a theory which may account for the fact that they are most effective at acid reactions.

The further evolution of the theories of antiseptics has been parallel to the evolution of the theories of enzyme chemistry. With the symbol of lock and key relationship, E. Fisher introduced forcefully, as P

Ehrlich had done with the theory of specific receptors, the concept that the structural configuration of the reacting molecules conditions the reaction between enzymes and substrates. This theory accounts for the extraordinary specificity of many biological phenomena. It explains in particular the phenomena of specific inhibition which have come to play such an important part in biochemistry, pharmacology, immunology, etc. Thus, in many cases, a given enzymatic reaction can be inhibited or blocked by substances which, because of the similarity of their molecular structure with that of the normal substrate, can react and combine with the enzyme, although they are not transformed chemically by it. Many examples of this type of reaction can be selected from the field of bacterial chemistry. For instance, succinic dehydrogenase is inhibited by compounds containing the group— CH_2COOH , notably by malonic acid, even though this compound is not “activated” by the enzyme. It has been shown that this enzymatic inhibition can result in retardation or inhibition of growth when malonate is added to a bacterial culture proliferating in a medium containing succinic acid as the sole source of carbon. By inhibiting the oxidation of the succinate, malonate deprives the organism of its source of energy. Although malonate acts as an inhibitor of bacterial growth in this system, it is not a cell poison, for it does not act as an inhibitor in systems where a preliminary oxidation of succinate is not necessary to provide the bacteria with carbon for synthesis.

The theory of competitive inhibition has found its most spectacular expression in the discovery that p-aminobenzoic acid can neutralize the bacteriostatic action of the sulfonamides. Sulfanilamide and p-aminobenzoic acid are closely related structurally, differing only in the fact that the sulfonic group of the former is replaced by a carboxyl group. In the latter, this relation suggested that the sulfonamides owe their antibacterial effect to their ability to compete, by virtue of similarity in chemical structure, with p-aminobenzoic acid in some essential metabolic reaction. It is not our purpose to examine whether this theory of “competitive inhibition” accounts completely for the mechanism of action of these drugs. It is worth mentioning, however, that there are facts which indicate the occurrence, during bacteriostasis, of a type of union between the aromatic amino group of the sulfonamide and some structure in the susceptible bacterial cell. Thus, when suspensions of *E. coli* are treated with dilute solutions of p-aminobenzoic acid, sulfanil-

amide, and related compounds, it is found that all the chemotherapeutically active sulfonamides have an effect on the electrokinetic mobility of the organism resembling that produced by the aminobenzoic acid, whereas the effect is quite different in the case of the inactive substances related to sulfanilamide. These facts suggest that the active drugs behave like p-aminobenzoic acid at the bacterial surface and that the association of the drug with the organism is a function of the aromatic amino group.

Bacteriostatic versus Bactericidal Effect It is to be expected that this initial primary reaction which takes place between the growth inhibitor and the homologous substrate (receptor) should in some cases be reversible under the proper conditions. For example, modifications of the acid-base conditions in the environment, removal from the medium of any excess of the antibacterial agent, addition of substances exhibiting a great affinity for it, should facilitate the dissociation of the complex formed between the inhibitor and the cellular substrate, and theoretically should restore the cell to a condition where growth again takes place.

Indeed, it has been possible in many cases to reverse the action of antiseptics commonly assumed to exert a bactericidal action. Cultures inhibited in their growth by the presence of a basic dye in a medium at slightly alkaline reaction can be caused to grow out by rendering the medium more acidic, thus decreasing the affinity of the dye for the acidic constituents of the cell. Bacteria "killed" with mercury can be caused to multiply again following treatment with soluble reduced sulfur compounds (H_2S , glutathione, thiolactic acid, cysteine, etc.) which exhibit great affinity for the metal. The phenomenon can be demonstrated with particular ease in the case of bacterial spores which, probably on account of their slow metabolism, can regain their viability after prolonged exposure to mercury when treated with sulfhydryl compounds. Another remarkable illustration of reversibility is found in the inhibition of growth of yeast and of *Lactobacillus casei* by a crystalline basic protein extracted from wheat. Although treatment of these microorganisms with the protein renders them unable to multiply, growth can be reinitiated by the addition to the system of different phosphatides. Since the basic protein is known to occur in wheat in combination with a phosphatide, it is possible that the reversal of antimicrobial action by the phosphatide is due to the formation of a lipoprotein which

helps in dissociating the basic protein from the cell

According to these views, the bactericidal character of an agent depends upon its ability to form with vital groups in the bacterium non-dissociable complexes. This requirement may account for the fact that surface activity and high molecular weight, two properties which favor the formation of insoluble or feebly ionized complexes, are so commonly found in bactericidal agents.

The ultimate effect, bacteriostatic or bactericidal, of a given agent is conditioned by a great variety of environmental factors among which can be mentioned the composition of the medium, its reaction, the temperature at which the test is carried out, etc. Of obvious importance is the nature of the microorganism involved. Thus, it is a matter of common observation that many agents are much more bactericidal for pneumococci than for streptococci. The nature of the microorganism influences the outcome of the antibacterial test, not only by determining the strength and stability of the combination between inhibitor and susceptible cellular substrate, but also because, during bacteriostasis, there occurs within the cell certain secondary changes which result in irreversible alterations and therefore, in death. The ease with which pneumococci undergo autolysis as soon as the medium becomes unfavorable for growth and multiplication accounts, in part at least, for the fact that many agents which are only bacteriostatic for other organisms exert upon pneumococci a bactericidal effect. The occurrence of secondary irreversible alterations during bacteriostasis may also explain the observation that the bacteriostatic effect of the sulfonamides can be converted into a bactericidal effect by raising the temperature at which the reaction is taking place from 37°C to 40°C. It is likely that, at the higher temperature, the rate of the catabolic reactions is increased while the compensatory anabolic reactions are inhibited by the drug. The more rapid exhaustion of some reserve substance, or the destruction of some essential structure may be the direct cause of the bactericidal effect.

It appears, therefore, that the difference between bacteriostatic and bactericidal effect is often of a quantitative rather than of a qualitative nature. It depends upon factors which affect the rate at which irreversible alterations go on within the inhibited cell, it is conditioned by the firmness of the combination between the toxic agent and its "receptor" in the susceptible cell, and by the ease with which the com-

bination can be dissociated

The Effect of Chemotherapeutic Agents on Bacterial Metabolism

The statement that a given antibacterial agent combines with a certain type of chemical group in the susceptible cell is not sufficient to define the cell structure and function with which it interferes. Thus, it is true that arsenicals and mercurials can combine with reduced thiol groups, these groups, however, are so widely distributed in the cell in the form of cysteine, glutathione, proteins, etc. and play a part in so many different metabolic events that the primary effect of the drugs on cellular structure or processes is not defined thereby. Similarly, the statement that basic antiseptics become attached to the cell at some acidic group does not describe the nature and function of the cellular groups which are affected.

As is well known, the similarity in molecular structure between sulfanilamide and its inhibitor p-aminobenzoic acid, has led to the formulation of the most widely quoted hypothesis attempting to account for the mechanism of drug action. It has been postulated that, in this case, the bacteriostatic action is due to a competition of the drug with p-aminobenzoic acid at some vital stage of metabolism in which the latter substance is concerned. Although there is as yet no direct convincing proof of the validity of this hypothesis, some evidence for it has come from the subsequent demonstration that p-aminobenzoic is indeed an essential growth factor or metabolite for many species. Moreover, indirect support for the theory of competitive inhibition has come from the fact that, by modifying the molecular structure of substances concerned in normal metabolism, it has been possible to synthesize a great variety of compounds which interfere with bacterial growth. Among many other examples, it is sufficient to mention pyridine-3-sulfonic acid, amino-sulfonic acids, thiopanic acid (pantoyltaurine), etc. which bear to nicotinic acid, amino-carboxylic acids, pantothenic acid, etc. the same relation that sulfanilamide does to p-aminobenzoic acid. All these sulfonic analogues of essential growth factors inhibit bacterial growth, and in all cases the inhibition of growth is reversed by the addition to the system of an excess of the corresponding normal carboxylic metabolite. Of special interest is the fact that one of these sulfonic compounds, thiopanic acid (pantoylthaurine) is capable under the proper conditions of behaving as a chemotherapeutic agent against streptococcus infec-

tion, and that this protective effect is neutralized by pantothenic acid

The increase in knowledge of the intimate processes of cellular metabolism has encouraged the investigation of the mechanism of drug action by the classical methods of metabolic chemistry. Many attempts are being made to determine, not only the effect of antiseptics and chemotherapeutic agents on intermediate metabolism, but also to identify more specifically the cellular catalysts and processes which are affected during inhibition. It must be emphasized, however, that there are few agents if any which are so specific in their action that they affect only one cellular structure or function, sulfanilamide for example, inhibits the enzyme carbonic anhydrase, but this fact is unrelated to the mechanism of its action on bacteria. In other words the discovery that a given antiseptic inactivates a certain enzyme or metabolic process is no evidence that this particular reaction is the one which determines the bacteriostatic or bactericidal effect. It is probably this lack of specificity, this multiplicity of biochemical activities exhibited by all antibacterial agents, which has prevented thus far the elucidation of the primary reaction which results in inhibition of growth or in death.

Antiseptic versus Chemotherapeutic Agents Granted these fundamental difficulties of interpretation, the analysis of the effect of antibacterial agents on the metabolism of susceptible cells has suggested a few generalizations concerning the characters which differentiate the ordinary antiseptics from the few substances which retain their activity *in vivo* and which can therefore, classify as chemotherapeutic agents. Most common antiseptics interrupt immediately and irreversibly the metabolism of living cells, whether it be measured in terms of oxygen consumption, production of carbon dioxide, production of acid, luminescence or other biological manifestation. In fact, measurement of the inhibition of these metabolic events has often been suggested as a quantitative method for the determination of antiseptic action and of the comparative activities of various agents. Let us consider on the other hand what little is known of the effect on metabolism of some of the few agents which have been found to retain their activity *in vivo*. There is still much argument concerning the intimate mechanism of the action of sulfonamides. It is certain, however, that these drugs do not completely interrupt cellular respiration, bacterial cells inhibited in their growth continue to metabolize even in the presence

of an excess of sulfonamides. Although no quantitative data have yet been published concerning the effect of penicillin on the metabolism of susceptible cells, it has been clearly stated that this drug does not affect the respiration of staphylococci. The comparative effect of gramicidin and tyrocidine is illuminating with reference to this problem. Both these substances are produced by cultures of *Bacillus brevis*, both are polypeptides in nature, both exhibit antibacterial activity. Tyrocidine is toxic not only for bacteria but also for all types of living cells so far tested and is therefore entirely ineffective *in vitro*, gramicidin, on the contrary, although toxic for spermatozoa and erythrocytes, is inactive against many other types of tissue cells, and among bacteria, affects chiefly the Gram-positive species. Interesting enough tyrocidine, like other common antiseptics, completely and irreversibly inhibits cellular metabolism, whereas gramicidin permits the maintenance, even though in a modified form, of oxygen consumption, of carbon dioxide and acid production, and of several other metabolic functions of even the most susceptible cells.

It appears, therefore, that whereas the typical antiseptic behaves as a gross protoplasmic poison, destroying the general metabolic and especially the catabolic cellular mechanisms, most chemotherapeutic agents have on the contrary, a very selective effect on some specific metabolic steps. The nature of the specific steps inhibited will undoubtedly vary from one chemotherapeutic agent to another. There are, for instance, observations which suggest that the primary effect of the sulfonamides is on some synthetic, anabolic, process. In the case of penicillin, it is reported that the drug does not in reality interrupt growth of the inhibited cell but prevents cellular division, with the frequent production of giant forms. Gramicidin appears to affect an energy-using process which would normally allow carbohydrate and phosphate storage. In other words, inhibition of growth can result not only from interference with the normal phenomena of respiration and nutrition, but also from the interruption of some process of synthesis, or of some step in cellular division. Since most of the knowledge of cellular metabolism available at the present time is limited to the catabolic processes which liberate energy, it is possible that no complete understanding of the mechanism of drug action can be reached until we know more of the methods by which the cell utilizes for growth and division the energy which it obtains from nutrition and respiration.

General Remarks Although the analysis of the phenomena of anti-sepsis has failed so far to reveal the precise nature of their mechanism, it has yielded information which permits a more rational statement of some of the practical problems of chemotherapy

The fact, for example, that many agents which are extremely active in artificial media lose much of their antibacterial activity *in vivo* or in the presence of animal tissues or fluids can be analyzed in terms of those factors which have been shown to affect the reaction between cell and antiseptic. Thus p-aminobenzoic acid and other substances which reverse the action of sulfonamides are produced by many cells and released during tissue breakdown, and undoubtedly play a part in rendering these drugs less active in the presence of exudates. This subject has been discussed so often in recent times that it need not be restated. There is another group of inhibitors of antimicrobial agents which deserve some mention at the present time. It has been observed that several types of phospholipids and a few other surface active substances are capable of protecting living cells against the lethal effect of the subsequent addition of many toxic agents, a fact of practical importance since phospholipids are commonly present in biological materials. It is possible that these compounds form inert complexes with certain basic antiseptics, also that they can exert a protective action by becoming absorbed on the cell surface, perhaps at the very sites at which the toxic agents would otherwise become absorbed.

There is still another type of substances which can inhibit antiseptics and chemotherapeutic agents, especially at the site of infected wounds and burns. We have emphasized earlier in this discussion that many of the antibacterial agents become attached to the parasitic cell through a combination of their basic groups with acidic cellular radicals. These same basic groups of the antiseptics also, probably combine with the acidic groups exposed at the surface of the tissues, for example those of chondroitin sulphuric acid, the carboxylic groups of various mucoids and of hyaluronic acid, the phosphoric group of nucleic acids, etc. All these acidic groups are present in complexes of high molecular weight, even of colloidal dimension. They may form feebly-ionized complexes with the basic antiseptics and by binding them at the tissue surface, they may render them useless from the antibacterial point of view.

Another fact worth considering in analyzing the reasons why so

many antibacterial agents are ineffective on infected wounds or burns is that the reaction of these tissues is often more acidic than that of the blood. It is a known fact, on the other hand, that most antibacterial agents become less active as the pH is lowered. One may wonder therefore whether the problem of infected wounds and burns will not demand that attention be directed toward a class of substances exhibiting an optimum zone of activity slightly on the acid side.

It has been pointed out that the common antiseptics and the chemotherapeutic agents seem to differ profoundly with reference to the effect which they exert on cellular metabolism. In contrast with general protoplasmic poisons, chemotherapeutic agents exhibit selectivity not only with reference to the type of cells which they affect but also with reference to the metabolic systems or structural constituents with which they react. This problem is not only of theoretical interest, but is also of immediate practical importance. Because of the cost and the labor involved in animal experimentation, many workers have attempted to develop short cut "screening" methods for the rapid evaluation *in vitro* of new antimicrobial agents. These *in vitro* methods often make use of inhibition of metabolism as measured by oxygen uptake, production of carbon dioxide or of acid, luminescence, etc. It is important to realize that, although these techniques would have been successful in detecting the gross protoplasmic poisons, they would have failed to recognize many substances of chemotherapeutic activity, sulfonamides would have been discarded as agents of little metabolic activity, penicillin would have been neglected in favor of the countless other phenolic compounds and quinones produced by molds, actinomycetes and bacteria, tyrocidine would have been selected in preference to gramicidin. The need for *in vitro* screening methods in the search for new chemotherapeutic agents is evident. It is clear, however, that none of the *in vitro* metabolic methods available at the present time are satisfactory. The development of new and adequate assay techniques, as well as the complete understanding of the intimate mode of action of chemotherapeutic agents, may have to await increased knowledge of the reactions concerned in anabolic metabolism and in the processes of growth and cellular division.

CHEMOPROPHYLAXIS OF
STREPTOCOCCUS DISEASE*

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CHEMOPROPHYLAXIS is a procedure involving the administration of drugs for the purpose of preventing certain infectious diseases in individuals or groups of individuals. The use of this procedure may be indicated when the probability of acquiring preventable infection is sufficiently great and when the hazards of such infection are of such magnitude as to justify the cost. In time of war the hazards of infection in military personnel are evaluated in terms of interference with the military mission, incidence of crippling disease and death rate. The military need for mass chemoprophylaxis which has been successfully met is the prevention or disruption of the training program. The cost of chemoprophylaxis may be stated in terms of the price of the drug, the time of the personnel necessary to supervise the administration and evaluate the results, the difficulties in discipline, and the frequency and seriousness of untoward reactions. Chemoprophylaxis was first given a place in clinical practice for the prevention of streptococcus disease and recurrence of rheumatic fever in individuals who had had previous attacks of rheumatic fever. This contribution was made independently and simultaneously by Doctors Caroline Thomas¹ and Alvin Coburn.² Sulfonamide prophylaxis was later used most effectively in the Army in prevention of meningitis³ and, on a small scale, to stop an epidemic of scarlet fever.⁴ The initiation of large scale chemoprophylaxis for streptococcus disease in the armed forces was again due to the interest of two officers in rheumatic fever—Commander Alvin Coburn⁵ of the Navy, and Colonel Paul Holbrook⁶ of the Army Air Forces, who independently made use of chemoprophylaxis for the purpose of pre-

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venting rheumatic fever in military personnel. Striking benefits of mass chemoprophylaxis beyond the effects on obvious streptococcus syndromes were observed in both programs. In this discussion we will deal with some of the problems and lessons of mass chemoprophylaxis as observed in the Navy and Army Air Forces and then see to what extent they may be applied to the problems of individuals.

Technique All the large scale programs of chemoprophylaxis have used sulfadiazine. There is clear evidence that daily administration is essential and that one dose a day given in the evening is highly satisfactory. One gram daily has been the most satisfactory dose. Regular administration of any drug daily to well people requires regimentation and organization. Responsibility for actual administration rests upon the officers in command of the military organizations. Adequate safeguards must be set up to see that cheating does not occur.

The Benefits of Mass Chemoprophylaxis The benefits resulting from different programs of mass chemoprophylaxis carried out in the armed forces have not been of the same magnitude. One of the most effective programs resulted in the prevention of nine out of ten attacks of scarlet fever, five out of six infections of the upper respiratory tract of sufficient severity to require hospitalization, virtually all meningococcus infections, and was effective in prevention of pneumococcus pneumonia and gonorrhea. The effect of mass chemoprophylaxis on the incidence of rheumatic fever differs from the effects on meningococcus infections and scarlet fever. It appears that during the first week of a program when the incidence of scarlet fever and meningococcus infections fall precipitously, the incidence of rheumatic fever may actually be increased, but after the first week reduction begins and, if the program is continued for a month or more, the results are impressively good.

The benefits to be derived from mass chemoprophylaxis in any group are related to the need for protection, thoroughness with which the program is carried out, and the care exercised in the prevention of untoward reaction. The decision to give protective drugs to a group of well people must be based upon an estimate that there is a great probability that these now healthy individuals will acquire a preventable disease during a limited period in the near future unless protection is provided. The estimate of danger to the group as a whole is based upon what is known to have recently happened to some members of the group. Prophecy of this sort is a function of the clinical epidemi-

ologist who is guided not by an inner light, but by quantitative data. Discussion of the indications for mass chemoprophylaxis is not within the scope of this paper. It will be dealt with authoritatively, and on the basis of his own brilliant work, by Doctor Coburn.

Forms of Streptococcus Disease The problems of diagnosis of streptococcus disease are such as to seriously complicate measures for their control. Streptococci cause certain highly characteristic syndromes such as acute tonsillitis, sinusitis, scarlet fever, peritonsillar abscess, acute otitis media, and pneumonia with empyema. A matter of the greatest importance in military and civil practice is the role of streptococci in certain nondescript forms of infection of the respiratory tract—nasopharyngitis, particularly. One of the most impressive effects of mass chemoprophylaxis in military personnel has been the remarkable reduction in incidence of disease of the upper respiratory tract severe enough to require hospitalization. It is not possible to say definitely at present what part the streptococcus plays in this group. It is generally believed that in the great majority of instances streptococcus disease of the respiratory tract is secondary to some virus infection such as common cold, measles, or influenza. It is encouraging to note in passing that during December 1943, there was an epidemic of influenza in military personnel. Although apprehension was felt, this outbreak was accompanied by relatively low incidence of severe forms of streptococcus disease. This influenza epidemic occurred fortunately, at a season when streptococcus disease is relatively infrequent and is usually mild. However this may be, in the light of Army experience in World War I it was very comforting to have available in this epidemic of December 1943 chemotherapeutic agents which are effective against the streptococcus.

Cost of Mass Chemoprophylaxis The financial expense of furnishing the drug for programs of mass chemoprophylaxis is insignificant. The cost in terms of untoward reactions is a matter of direct concern and responsibility to the clinician. It is the responsibility of the physician to weigh the probable benefits of chemoprophylaxis against the hazards of untoward reactions. From the experience of mass chemoprophylaxis in the armed forces to date, it is clear that the hazards of untoward reactions can be kept to an insignificant minimum, but if civilian and military physicians do not familiarize themselves thoroughly with the peculiar dangers of the combination of prophylactic and therapeutic

use of sulfonamides, if they are careless in the use of this information, disastrous intoxication will occur which may discredit this valuable procedure of preventive medicine and bring down justified criticism of the medical profession. Harmful reactions to prophylactic doses only, do not include renal complications due to crystalluria—the problem is entirely one of sensitivity. Evidences of a sensitivity reaction may be expected in from four to five individuals out of each 1000. These are mild reactions and are of little importance if the drug is stopped soon after their appearance. Severe reactions which are dangerous to the life of the individual may occur in one out of 100,000 individuals from prophylactic doses only. Most sensitivity reactions appear during the second week of the program. The appearance of fever in from two to four hours after a dose of sulfonamide is one of the common manifestations of sensitivity. Unfortunately, thermometry does not lend itself to routine use in large groups of military personnel on a duty status. With few exceptions, the first distinctive evidence of sensitivity reaction is the appearance of skin eruption. In 95 per cent of patients showing skin rash the lesions may be described as morbilliform, erythematous, urticarial, or papular. The rare forms of skin lesions are those of photosensitization, fixed eruption, exfoliative dermatitis, and purpura.

Therapeutic Disasters A large percentage of severe sensitivity reactions which have developed in those receiving chemoprophylaxis have followed the administration of therapeutic doses of sulfonamides when manifestations of sensitivity to the drug were diagnosed as conditions for which sulfonamide therapy was believed indicated. These mistakes have been mainly as follows:

1. Fever and chilliness due to sensitivity, but assumed to be caused by pneumonia.

2. Scarletiform rash diagnosed as scarlet fever. Sensitivity rash can nearly always be differentiated from scarlet fever by clinical features alone.

3. Tonsillar or pharyngeal lesions diagnosed as acute streptococcus infection, when actually a manifestation of agranulocytosis.

Transfusion of individuals because of the presence of agranulocytosis resulting from sulfonamide sensitivity, with blood from a donor receiving chemoprophylactic doses of sulfadiazine, has led to reactions of extreme severity. The disastrous consequences of therapy with sulfonamides of the sort described above can be eliminated only when

physicians acquire the fixed habit of never prescribing sulfonamides in therapeutic doses until they have satisfied themselves that the condition under treatment does not represent, even in part, a manifestation of sensitivity to sulfonamides. In every instance fever and skin rash should be first suspected as due to sulfonamides.

It is the responsibility of the medical profession, civilian and military, for complete elimination of this group of severe reactions. The responsibility of civilian physicians must be emphasized, because some of the severe reactions have been precipitated by therapy prescribed by civilian physicians to military personnel while on furlough.

The following suggestions are offered as safeguards against serious reaction:

1. Thorough education of medical personnel as to the nature of sensitivity reactions to sulfonamides, and the unique dangers of therapy which arise from programs of prevention.

2. Each individual before beginning chemoprophylaxis should be called upon to report any untoward reaction to previous sulfonamide therapy.

3. Responsibility should be placed upon the individual for reporting the appearance of rash. Individuals who report subjective symptoms which follow the administration of the drug, such as flushing of the skin, feverishness, and pruritus, should be checked by thermometry.

4. Medical supervision should be adequate for early diagnosis of sensitivity reaction and elimination of the individual from the program.

5. Determination of the white blood count whenever there is any basis for suspicion of agranulocytosis and, in every case, before the administration of therapeutic doses of sulfonamide.

6. If penicillin is available, therapy with sulfonamides should be absolutely contraindicated for any individual known or suspected to have recently received sulfonamide for chemoprophylaxis if he manifests rash or leukopenia.

Prophylaxis for the Individual. Information is not yet available which permits evaluation of the extent of protection afforded to the individual in programs of mass chemoprophylaxis by the drug which he himself takes, and the protection due to the fact that others in his environment are also receiving the drug. It is entirely possible that a larger dose would be necessary to protect a single individual in a given epidemiologic situation than if all individuals in the group received the

drug Furthermore, we must bear in mind that the studies on military personnel dealt with a highly selected group of young men within a narrow age range with a state of physical fitness far beyond that of the average civilian population When chemoprophylaxis is attempted in individuals in poor general health, and particularly in the older age group, it is not unlikely that greater difficulties may be encountered with toxic manifestations What principles should guide the practicing physician in the use of chemoprophylaxis for individual patients? We would suggest that two considerations are of importance in evaluating the need of individuals for chemoprophylaxis

- 1 Membership in a group in which there is an epidemic and when mass chemotherapy or chemoprophylaxis is not available No doubt there are situations in civilian groups that resemble, in many important respects, the epidemic conditions of military life

- 2 We should consider the possibility of giving protection to those individuals who are prone to frequent severe disabling respiratory infections For example, individuals with sinusitis, bronchitis or bronchiectasis are commonly asymptomatic until a common cold ushers in a severe incapacitating illness

The greatest opportunity and responsibility for the use of chemoprophylaxis in individuals is for those who have had attacks of rheumatic fever The evidence is clear that crippling heart disease from rheumatic fever is, in the main, the result of repeated attacks of rheumatic fever and repeated attacks can be prevented by chemoprophylaxis The optimum dose for individuals has not been established, but 1 gram daily of sulfadiazine is worthy of extensive trial Close medical supervision is of the greatest importance during the first four weeks of chemoprophylaxis, with a check in leukocyte count and for febrile or skin reactions at least twice a week during this period If sensitivity reactions do not appear during the period, it is unlikely that they will occur as long as the drug is taken continuously The desirability of continuous year-round chemoprophylaxis in such individuals is based on three considerations

- 1 Taking the sulfadiazine should become a rigid habit, unbroken by a summer lay-off

- 2 The dangers of sensitivity reaction are greatly increased by intermittent use of sulfa drugs

- 3 Although streptococcus disease of great severity is rare during

the summer months in most communities, mild infections sufficient to reactivate a rheumatic process are not uncommon. The use of chemoprophylaxis in individuals who have had rheumatic fever is obviously not for use by the impatient physician who demands a maximum of results in the shortest time. It requires the greatest understanding of the personal problems of the individual, and the greatest capacity to persuade the individual to cooperation and self-discipline over a long period of time without arousing such anxiety as to counterbalance the good effects to be obtained.

Summary We may say that chemoprophylaxis is a new and not fully evaluated tool of preventive medicine, but is proven to have great potentialities for good when properly used in groups or for individual patients. This new technique for use of drugs offers new opportunities and forces new responsibilities on the medical profession. The use of chemoprophylaxis in military medicine requires that a physician try to master the art of diagnosis and prognosis of infections as applied to groups so that it may be prescribed wisely. The most direct and immediate responsibility is for minimizing untoward reactions. This responsibility can be met when every doctor, civil and military, familiarizes himself with the clinical manifestations of sensitivity to sulfonamides when he recognizes potential disaster which may result from mistaking the manifestations of sensitivity to sulfonamides for conditions which may be benefited by therapy therewith. It is necessary that doctors assume a persistent attitude of intelligent suspicion that clinical manifestations formerly considered innocuous may now be warnings that the patient is susceptible to the greatest harm by the best-intentioned use of an extremely valuable drug.

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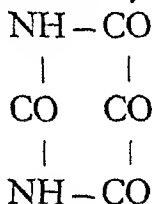
ALLOXAN DIABETES ITS PRODUCTION AND MECHANISM*

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A LLOXAN DIABETES IS a new type of experimental diabetes. It is a chemical diabetes caused by treatment with an organic compound, which is related to physiological body substances. It can be produced in the intact animal and in many species. Its signs and symptoms are identical in many respects with those of human diabetes. It is the purpose of this paper to describe the production and the patho-physiology of this diabetes and to compare its mechanism with that of the various other types of experimental diabetes.

Alloxan has been known for more than 100 years, since Woehler produced it by oxidation of uric acid. It has the following structure:



is a colorless powder, melting at 256 degrees centigrade, and is easily soluble in water and alcohol. It decomposes on hydrolysis into urea and mesoxalic acid. Alloxan reduces to dialuric acid with which it acts as an oxidation-reduction system, and its structure is found as a constituent part of the flavine molecule. It has been found to produce profound disturbances in sulfur metabolism, to enhance the endogenous metabolism of liver suspensions, and to be a capillary poison. In spite of this, little evidence exists so far that alloxan plays a role in physiological processes. Uric acid metabolism, so far as is known, does not seem to involve alloxan even as an intermediary product.

The discovery of the diabetogenic action of alloxan is accidental.

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as many other great discoveries in science. It is the great merit of the English pathologist Shaw Dunn, whose recent death put an untimely end to a distinguished career, to have observed that alloxan had a specific necrosing action on the cells of the islets of Langerhans. Working on the crush syndrome and the effect of ureides on the kidney, he and his co-workers made this "side observation" and called attention to its importance. Six years earlier, in 1937, Jacobs¹ had found that the injection of alloxan into rabbits resulted in an initial hyperglycemia which was soon succeeded by a severe hypoglycemia, lasting up to eight hours or longer, and terminating with death of the animals unless glucose was administered. All his experiments, however, were acute, and no histological studies were done. Dunn, Sheehan and McLetchie,² noticed again this fluctuation of blood sugar in alloxan-treated animals, recognized its relationship to the accompanying anatomical islet cell damage and though their rabbits had all died in a few days, suggested that a sustained diabetes should be the final result of alloxan poisoning.

Their report stimulated work by other investigators, and in only a few months, alloxan diabetes was demonstrated in various animal species. In July, 1943 the production of alloxan diabetes in dogs, and of transitory hyperglycemia and glycosuria in rabbits was announced from our laboratory.³ Bailey and Bailey reported on alloxan diabetes in rabbits,⁴ and Shaw Dunn and his group⁵ produced alloxan diabetes in the rat. In the meantime, confirmations and further contributions have been made by several workers in this country and abroad.⁶⁻⁹

The diabetogenic doses

In our laboratory the diabetogenic effect of alloxan has been studied in the dog, the rat, the cat, the rabbit, the rhesus monkey, the pigeon, and the guinea pig.¹⁰⁻¹⁴

Alloxan diabetes can be produced with one single injection of alloxan. We use freshly prepared unneutralized 5 per cent solution, and give it intravenously or intraperitoneally because of its decided acidity. Neutralization inactivates alloxan, and it decomposes on standing. Scattered small doses and subcutaneous injections have been used also with success.

We define the diabetogenic dose as the amount of alloxan which in eighty per cent of the animals of a given species will produce sus-

tained hyperglycemia and necrosis of the pancreatic islet cells, but which will not cause observable damage to other organs

TABLE I

Diabetogenic Doses of Alloxan in Various Species

Rat	200-300 mg/kg 1 p
Rabbit	100-200 mg/kg 1 v
Cat	150 mg/kg 1 v
Monkey	100-150 mg/kg 1 v
Dog (dalmatian hound)	50-100 mg/kg 1 v
Pigeon	125-200 mg/kg 1 v

Table I shows the doses as we have found them for various species. It must be mentioned, however, that the response of the cat is very erratic and that of the pigeon develops other metabolic changes frequently, which will be discussed later.

The greatest sensitivity and smallest required dose are found in dogs. Next in sensitivity are monkeys, pigeons and cats, rats and rabbits require the largest dose. The carbohydrate metabolism of the dalmatian hound and the pigeon, which, like man, do not convert uric acid into allantoin, responds in the same way as the animals do which produce allantoin from uric acid.

If a dose larger than the diabetogenic dose is given, severe kidney damage is produced also, and anuria and nitrogen retention develop, and the animals succumb in a few days in a uremic-diabetic syndrome. Still larger doses are fatal within a few hours, probably because of the effect of alloxan on the circulatory system, there is evidence of acute pulmonary edema. The margin between the fatal, the uremic and the diabetogenic dose is the widest in rabbit, rat and dog, smaller in the monkey, and smallest in pigeon, cat and guinea pig. In the latter, no exact diabetogenic dose could be established as yet, since degenerative lesions in the pancreas were found only in those animals which died within 24 hours after injection of alloxan.

The clinical course

Typical diabetes mellitus will develop about 24 to 28 hours after the injection of a diabetogenic dose of alloxan. The classical signs and symptoms of hyperglycemia, glycosuria, polyuria, and polydipsia will

be present, and very frequently polyphagia and loss of weight. In some species early ketonuria can be observed.

During the first day after the injection, careful observation and supervision are necessary in rabbits and monkeys, lest they die in hypoglycemic convulsions. Frequent administration of glucose may be required. Dogs, rats, and pigeons show less marked initial fluctuations of the blood sugar, and may survive without protection by glucose.

Dogs with alloxan diabetes appear well for about two to three weeks. Their blood sugar remains at a level between 200 and 300 mg per 100 cc., and their glycosuria may reach four to seven per cent. They eat with great appetite and lose little weight during this period. Glucose tolerance tests show a typical diabetic curve, and insulin sensitivity tests prove that the animals are sensitive to insulin from the very beginning of their diabetes.

Under insulin treatment, the dogs remain in good condition for many months. About one unit protamine zinc insulin per kilo per day is necessary to prevent loss of weight, to maintain normal fasting blood sugar, and to keep the urine free or almost free of sugar. If the dogs remain untreated for more than two or three weeks, they stop eating, lose weight rapidly, appear weak, listless and drowsy, and are very susceptible to infections. This condition is accompanied by the development of hyperlipemia and fatty degeneration of the liver, a phenomenon which may be of importance for the problem of lipocae, since—as will be shown later—the alpha cells remain intact in alloxan diabetes. The diabetic symptoms very seldom show spontaneous improvement, and usually persist until death occurs in complete emaciation at six to seven weeks.

Monkeys have a very high blood sugar and marked glycosuria following the initial hypoglycemia, ketonuria is present very early. The monkeys look sick and depressed, become emaciated rapidly, and go into acidosis. This is remarkable since monkeys who have been pancreatectomized do not always develop severe diabetes.

Rats, too, show a rapidly progressing diabetes and die in ketosis and acidosis in six to nine days if untreated. Out of a series of 27 rats, which we injected with alloxan, only four did not develop diabetes. All the others showed marked glycosuria and hyperglycemia within 24 to 48 hours. The blood sugar reached values of 300 to 500 mgm per cent. On the third or fourth day, ketonuria appeared in those animals whose

blood sugar was higher than 300 mgm per cent. Most impressive was the polyuria; the daily urinary output often exceeded 10 per cent of the body weight. The weight loss averaged 30 per cent in six days. Insulin treatment controls this alloxan diabetes.

The alloxan diabetes of the rabbit also responds to insulin therapy, but its course in the untreated rabbit may take two entirely different forms.

Some animals react, as do dogs, rats and monkeys, and lose weight rapidly, become seriously emaciated, and die within a week. Their blood sugar level is between 400 and 500 mg per cent, and there is a 5 to 10 per cent glycosuria.

Another group of rabbits respond with similar levels of blood and urine glucose, but after an initial slight weight loss seem to recuperate and regain their weight, appearing in excellent health. Such animals survive without insulin treatment for months, despite the severe diabetes and are apparently capable of compensating for the loss of glucose in the urine by increasing their food intake.

A few rabbits may give the impression of clinical cure of the diabetic condition, the blood sugar returns to normal, the urine is 'sugar free', but a persistently decreased glucose tolerance test remains to indicate the diabetes.

Of great interest is the development of systemic changes usually considered secondary to diabetes. The great susceptibility to infections has been mentioned before. Of greater importance is the development of cataract which has been observed first by Bailey¹⁵ and of retinitis which was reported by Lewis. It seems, however, that other factors besides the diabetes may contribute to these eye complications. They are not found in all alloxan diabetic animals, and have not yet been observed in our laboratory. So far we have no explanation for this surprising fact.

Pigeons which after total pancreatectomy usually do not develop hyperglycemia and survive indefinitely, respond to alloxan injection with an elevation of the blood sugar to 400 or 500 mg per 100 cc. They appear sleepy, weak and drowsy, and sit with their eyes closed, making no attempt to move or fly, and die in this stupor. Death, however, may not be due to the diabetes alone, many of the animals develop a very interesting second condition, which has been known for a long time as visceral gout. The blood uric acid content shows a marked

increase to 100 times the initial level and at autopsy, the pericardium and other serous membranes are found to be covered with sodium urate crystals, the kidneys are infiltrated with the same material

The histological changes

Only a few remarks on the histological changes after alloxan treatment, which will be dealt with in detail in the following paper by G Gomori. The pancreatic changes are practically identical in all species mentioned and are characterized by a selective necrosis of the beta cells, as has been shown first in our laboratory, not of the whole islet system. Whereas the beta cells undergo rapid degeneration and disappear finally completely, the alpha cells remain undamaged, at least retain their normal staining property. The beta cell necrosis proceeds without any sign of inflammatory reaction. In dogs the pancreatic ducts usually show a characteristic vacuolization. Of extra-pancreatic changes, the glycogen deposition in the kidney, accompanying pronounced glycosuria, and the necrosis of the convoluted tubules are of importance, the latter occurring only if amounts larger than the diabetogenic doses have been given. The fatty infiltration of the liver, which is most marked in the dog, has been mentioned before. How rapidly the islet cell necrosing action of alloxan starts and how quickly alloxan is made innocuous or removed from the blood stream could be demonstrated recently in the following, not yet published, experiment. We deprived part of the pancreas of its blood supply by means of a clamp, which was released five minutes after the injection of alloxan. Biopsies were taken 24 hours later from both parts of the pancreas and showed that the islet cells appeared essentially normal where the circulation had been interrupted for five minutes only, and that the rest of the pancreas which had had normal blood supply had undergone the typical beta cell degeneration.

The mechanism

If the degeneration of the beta cells leads to deficient insulin production and thus to diabetes, bioassays of the pancreatic tissue should reveal changes in the insulin content. Assays were carried out on the pancreas of three dogs with alloxan diabetes of a duration of 18, 30, and 60 days. In all three, the insulin content of the pancreatic tissue was markedly decreased. Whereas the pancreas of a normal dog con-

tains about 2 to 3 units of insulin per gram, only $\frac{1}{4}$ of this amount was recovered from the alloxan-treated organs. This seems to be conclusive evidence that alloxan diabetes is a true pancreatic diabetes and is the result of insulin deficiency. This experiment has found confirmation recently in the work of Ridout, Ham and Wrenshall.¹⁶

How does alloxan exert its effect upon the islet cells?

Let us recall the early blood sugar fluctuation after alloxan: first a short-lasting hyperglycemia, then a transitory hypoglycemia which in the rabbit frequently requires treatment with glucose, and finally the sustained diabetic hyperglycemia. What is the cause and the significance of these three phases? We shall discuss first the hyperglycemia as a whole, then the initial hyperglycemic phase alone, and finally the hypoglycemia. It is known from the surgical diabetes after partial pancreatectomy, as well as from anterior pituitary diabetes that the initial hyperglycemia precedes the islet cell degeneration and that diabetes will not develop if the hyperglycemia is prevented by starvation, insulin treatment or phlorhizin injection.¹⁷ Here the hyperglycemia is a causal factor of the ensuing diabetes.

In alloxan diabetes such protection is not possible. The diabetogenic process will take its course regardless of whether the initial hyperglycemia is prevented or not. Alloxan affects the islets cells directly.

In a series of experiments which can only be summarized here, we have been able to show that treatment with phlorhizin as well as treatment with insulin will prevent the initial alloxan hyperglycemia, but in spite of the normal blood sugar level the islet cell degeneration will develop. Two dogs were treated for a period of ten days with phlorhizin, on the eighth day they received a diabetogenic dose of alloxan. Diabetes developed as if no phlorhizin had been given. Another dog was given insulin together with and four days following the injection of alloxan. As soon as insulin treatment was discontinued, a marked hyperglycemia and glycosuria became evident. Diabetes had developed as if no insulin had been given. Insulin treatment was renewed after a few days. The same dose was sufficient for diabetic control, there was no change in the sensitivity to insulin. When after a week insulin was stopped, the diabetes became evident again, and a biopsy of the pancreas revealed islet cell degeneration to the same extent as in animals not treated with insulin at all.

Now the early hyperglycemic phase. If insulin is injected together

with alloxan—either as a mixture into the same vein, or separately into different veins—no initial hyperglycemia will develop in the rabbit. The hypoglycemic phase, however, is of the usual severity, and diabetes results as if alloxan alone had been given. The fact that insulin prevents the initial hyperglycemia argues against the possibility that the mechanism is one of insulin inhibition. This possibility was ruled out further when we found that insulin was not inactivated by alloxan *in vitro*. It seems, therefore, likely that the initial hyperglycemia is not due to lack of insulin, but to mobilization of extra glucose. Such glycogenolysis might be produced by the liver under the influence of epinephrine.¹⁸ As a matter of fact, Young and his associates⁹ were able to reproduce the initial alloxan blood sugar curve by the injection of adrenalin and insulin into normal rabbits. We subjected this hypothesis to experimental test by the injection of alloxan into functionally or anatomically adrenalectomized rabbits. The adrenals were extirpated surgically or the medulla was destroyed by intramedullary injection of formalin. A diabetogenic dose of alloxan was given immediately after the removal of the second adrenal or two days after the formalin injection. In no instance did any marked initial hyperglycemia develop. All animals went into severe hypoglycemia and in the few surviving animals diabetes developed. It can be concluded from this experiment that adrenal stimulation of gluconeogenesis is involved in the production of the initial alloxan hyperglycemia. This conclusion is supported by the evidence of histological changes in the adrenal medulla immediately after alloxan injection given by Hard and Carr.⁸

The second phase of the blood sugar reaction to alloxan, the hypoglycemia, was originally interpreted as a result of an insulin-like effect of alloxan itself. Were this true, the blood sugar of depancreatized animals should fall in response to alloxan. We gave diabetogenic doses of alloxan to depancreatized dogs and also to rabbits which previously had been rendered diabetic by alloxan. No lowering of the blood level could be noted in either group. The presence of a normally functioning pancreas, therefore, seems to be necessary for the occurrence of the hypoglycemic reaction, and it would appear that alloxan changes glucose metabolism through its effect on the pancreatic islet cells. This conclusion is further substantiated as well by the work of Corkill, Fantl and Nelson,⁷ who found that alloxan did not influence the blood sugar level of the eviscerated cat, and by Ridout and his co-workers

who worked on depancreatized dogs¹⁶

If the hypoglycemia is brought about by the effect of alloxan upon the pancreas, it may be caused either by islet cell stimulation or by the release of stored insulin from the degenerating cells. The first view, put forth by Dunn and his co-workers,^{2, 5} suggests that increased islet cell activity and overproduction of insulin may overstrain the cells and cause their subsequent failure and degeneration. The experimental evidence, however, seems to favor the second possibility, and we believe with Young and his co-workers⁹ that the hypoglycemia is the first sign, rather than the cause, of the developing necrosis. We base our belief on the following evidence:

1. Beta cell degeneration precedes the hypoglycemia. In histological studies on rabbits and dogs we have found that beginning degeneration of the beta cells is demonstrable as early as one hour after injection with alloxan. It precedes the hypoglycemia which usually develops only after four to five hours.

2. It is impossible to separate the hypoglycemic effect from the diabetogenic action. Whenever hypoglycemia develops, diabetes follows if the animal survives.

The specificity of alloxan

A few words must be said about the remarkable specificity of alloxan as a diabetogenic agent. Dunn and his co-workers² had found that not only alloxan but also a quinoline compound (styryl-quinoline No. 90) produced islet cell necrosis in rabbits. They tested several other compounds as oxalic acid, uranium, guanidine and uric acid, and found that none of them had a diabetogenic or islet cell necrosing effect. Earlier Jacobs^{1, 19} had found that none of a series of more than sixty chemical compounds produced the fluctuation of the blood sugar level which is characteristic for early response to alloxan. No alloxan-like action was found in a series of compounds tested by Thorogood.²⁰ We have tested three groups of substances: compounds which are chemically related to alloxan, such as dialuric acid, the reduction product of alloxan, and alloxantin, which is formed by interaction of alloxan and dialuric acid; oxidizing agents, which were tested on the assumption that alloxan may owe its effect to its oxidizing property; and quinoline and cinchophen as relatives of styryl-quinoline, which is not available on the market. These substances were injected in various doses in dogs

and the blood sugar level as well as the histological appearance of the pancreas were followed. None of them exhibited any diabetogenic activity though several of them proved to be very toxic. The specificity of the diabetogenic action of alloxan, therefore, remains unexplained. It seems, however, unlikely that its oxidizing property is the diabetogenic factor.

Comparison with other forms of experimental diabetes

In a comparison of alloxan diabetes with other forms of experimental diabetes it must be pointed out once more that the diabetes of alloxan poisoning is the result of *direct* damage to the beta cells. This chemical diabetes thus differs significantly from the surgical diabetes of partial pancreatectomy and from the endocrine diabetes of treatment with anterior pituitary extract (APE diabetes)^{21,22} though all three have in common the degeneration of the beta cells. This difference can be summarized as follows:

- 1 Both surgical and APE diabetes are considered to be due to overwork of the beta cells since they can be prevented by starvation or by insulin in the early stages of the disease. Alloxan diabetes is the result of direct action upon the islet cells and cannot be prevented either by starvation or by insulin.

- 2 The pituitary extract has to be administered in increasing doses over a period of several days, while alloxan is effective in a single dose.

- 3 Some species, as for instance, rats, can be made diabetic by APE only after extensive resection of the pancreas, while alloxan is effective in the intact animal.

- 4 APE diabetes in its early stage is insulin-resistant while alloxan diabetes is not.

- 5 The histologic changes in APE diabetes are mitoses, degranulation and vacuolization of the beta cells with subsequent atrophy and hyaline changes. In alloxan diabetes the changes are those of an irreversible acute degeneration, without vacuolization or fibrosis.

It must be emphasized further that alloxan proved to be diabetogenic even in those species in which total pancreatectomy is not always followed by severe diabetes.

What the significance of alloxan diabetes may be for the pathogenesis of human diabetes must be left for further investigation. Whatever the outcome may be, it can be stated already that we have found

in the diabetogenic action of alloxan not only new means to study disturbed carbohydrate metabolism but also a previously unknown mechanism which causes beta cell degeneration and diabetes through the toxic effect of an organic compound related to protein metabolism

Therapeutic implications

Finally, attention should be called to a clinical implication. Brunschwig^{23,24} has suggested that the islet cell-necrosing property of alloxan might be of use in the treatment of hyperinsulism and islet cell tumors. He gave alloxan to a few patients with inoperable carcinoma and to one patient with metastatic islet cell tumor. The clinical results which we observed with him were not very striking, and the histologic changes in the islet cells were surprisingly slight. The observations, however, are too limited to permit conclusions as to the advisability and effectivity of such treatment. The fact that many animal species have been found sensitive to the islet cell-necrosing action of alloxan makes it likely that man will be no exception. In any case, the remarkable—and almost unique—fact of the specific action of a chemical compound on a highly differentiated specific cell system deserves greatest interest and thorough examination.

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Editor's Note

A related paper by Dr George Gomori, Department of Medicine, The University of Chicago, entitled "The Histology of the Normal and Diseased Pancreas," which was presented before the New York Diabetes Association, September 28, 1944, will appear in the February issue of the Bulletin together with a discussion of these two papers by Dr Paul Klemperer, Pathologist, The Mt Sinai Hospital, New York

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BULLETIN OF
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FEBRUARY 1945

THE COMBINED USE OF ANTI-INFECTIVES
AND ANTICOAGULANTS IN THE
TREATMENT OF SUBACUTE BACTERIAL
ENDOCARDITIS* † **

LEO LOEWE

THE subject of subacute bacterial endocarditis requires few introductory remarks before an audience of The New York Academy of Medicine. Since 1906 and culminating with the publication of his monograph¹ in 1941, Emanuel Libman has described the clinical syndrome in all of its ramifications and clearly delineated the difficulties imposed upon the therapeutic attack, he established the fact that the disease, with few exceptions, was of streptococcal origin, he demonstrated, as far back as 1910, that it was possible to obtain positive blood cultures in 73 of his first 75 cases, he astutely assumed that the portal of infection was "about the teeth or their roots, the tonsils and accessory sinuses or other parts of the upper respiratory tract," he stressed the importance of the previously existing valvular defect, whether acquired or congenital, as a predisposing factor in the production of the disease, he described fully the usual and the bizarre pathological changes asso-

* Presented at the Seventeenth Graduate Fortnight of The New York Academy of Medicine, October 18, 1944.

† From the Department of Medicine and the Department of Laboratories, Jewish Hospital, Brooklyn, N. Y. Aided by grants from Friends of the Hospital and the Dazian Foundation for Medical Research.

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ciated with the disease, he emphasized, throughout his clinical thesis, the pathognomonic features particularly referable to the eruptive phenomena, changes in skin color, the frequent embolic complications and the wide range of forms in which the disease might masquerade

Early in the course of his studies, Libman recognized that severer forms of the disease occasionally progressed to spontaneous recovery and estimated that this happy outcome was encountered in at most three to five per cent of the afflicted, he also recognized that there was a milder or bacteria-free stage of the disease in which the patient might not be seen until recovery had occurred Emanuel Libman noted that an occasional recovery was reported using any one of a variety of chemotherapeutic or physiotherapeutic modalities With his usual perspicacity, he cautioned that the lack of consistent effect from any one given remedial agent suggested that the isolated "cure" may have been more likely an instance of the spontaneous recovery that is occasionally noted in the severe forms or an example of the milder bacteria-free syndrome

Emanuel Libman's monograph concludes with the statement of the status of therapy in 1941, in his own words, I quote, "at the present time, therapy in subacute bacterial endocarditis remains unsatisfactory

A chemotherapeutic agent more effective on the streptococcus viridans than any at present available is needed and may be found,

The future looks more promising than ever before"

It is my purpose this evening to add a chapter to Libman's monograph, we shall present data which indicate that combined therapy using an anti-infective agent and an anticoagulant produced what appears to be clinical cure in approximately 75 per cent of a consecutive series of 54 unselected patients

LABORATORY DATA

The basis of the present clinical investigation is dependent upon experimental thrombotic bacterial endocarditis as it was produced in the rabbit in collaboration with my colleagues Rosenblatt and Lederer² This work indicated that fibrin and blood elements served as an impenetrable barrier to effective chemotherapeusis, the offending organisms, lying deep in the vegetation, were well protected from circulating anti-infective agents To accomplish disappearance of vegetations, the combined use of a suitable chemotherapeutic agent and an anticoagulant

was required Heparin was successfully employed, in these experimental animals, to arrest the deposition of blood platelets and fibrin which served as a protective nidus and as a stimulus for bacterial growth, relatively fresh, artificially induced thrombi in the animal could be dissipated following the use of the anticoagulants In corroboration of the experimental investigations, were observations obtained from human post-mortem material which indicated that heparin has a possible erosive effect on endocardial vegetations³

EVOLUTION OF THE CLINICAL STUDIES

The attempt to translate experimental investigation into terms of clinical therapeutics was at first disappointingly unsuccessful The intravenous administration of heparin was fraught with danger and the expense was prohibitive in many instances Whether given by continuous venoclysis or fractional intravenous injection, heparin therapy was cumbersome, accompanied by severe reactions and associated with treatment deaths in altogether too many instances to justify its continuance⁴ To overcome these shortcomings, a special method⁵ was devised for the subcutaneous deposition of the drug, through adoption of the Pitkin menstruum, composed of gelatine, dextrose, glacial acetic acid and water in definite proportions, which was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously By this technique, a slower and more equable absorption of heparin was accomplished

When this portion of the clinical technique had been solved, a combined attack was inaugurated using the sulfonamides in association with the heparin A group of seventeen patients with subacute bacterial endocarditis was treated but there was no more than two apparently authentic "cures"—insufficient to justify the conclusion that a specific therapeutic result had been obtained beyond what might be noted with the occasional spontaneous cure or the development of Libman's bacteria-free state Nevertheless, the two successful issues were sufficient to justify a continued project, more particularly since one of the necropsied cases showed an apparent diminution in the size of vegetations which were smaller and more discontinuous than might have been anticipated

With the introduction of penicillin therapy, we were sufficiently fortunate to obtain supplies through the courtesy of Mr John L Smith

TABLE I
USE OF HEPARIN IN PENICILLIN ASSAYS
Experiment #1 (1-4-44)

	<i>ml Penicillin Solution</i>			<i>mg Heparin</i>	<i>mg Heparin-O U ratio in 10 ml</i>	<i>Series-Dilution Test Results</i>
A	9	+	0.5 in 1 ml	H ₂ O	0.5 mg / 1,120 O U	124 O U / ml
B	9	+	1.0 " " "	"	1.0 " " "	145 " "
C	9	+	5.0 " " "	"	5.0 " " "	145 " "
D	9	+	10.0 " " "	"	10.0 " " "	124 " "
Control	9	+	1.0 ml	H ₂ O		126 O U / ml

Experiment #2 (1-8-44)

	<i>ml Penicillin Solution</i>			<i>mg Heparin</i>	<i>mg Heparin-O U ratio in 6 ml</i>	<i>Series-Dilution Test Results</i>
A	5	+	0.5 in 1 ml	H ₂ O	0.5 mg / 640 O U	128 O U / ml
B	5	+	1.0 " " "	"	1.0 " " "	128 " "
C	5	+	5.0 " " "	"	5.0 " " "	135 " "
D	5	+	10.0 " " "	"	10.0 " " "	128 " "
Control	5	+	1.0 ml	H ₂ O		128 O U / ml

of the Charles Pfizer Company and later, also, through the cooperation of the Committee on Penicillin Therapy of the National Research Council under the aegis of Dr Chester S Keefer. The technique was modified by the replacement of sulfonamide with penicillin, continuation of subcutaneous depositions of heparin was made possible by the cooperation of Ralph D Shaner and Leo Pirk of Roche-Organon, Inc, which company gratuitously furnished all heparin preparations.

As a preliminary to the inauguration of penicillin-heparin therapy, experiments were devised to determine the effects of heparin on solutions of penicillin. The data (Table I) indicated clearly that the anti-coagulant had no measurable effect on the anti-infective potentialities of the penicillin, indeed, there was some suggestion of possible synergism or potentiation.

DOSAGE SCHEDULE

The administration of heparin and the determination of optimum

TABLE II
TREATMENT STATISTICS—SUMMARY

<i>Dosage</i>		
Penicillin sodium salt (Oxford units)		
	<i>Range</i>	
	<i>Low</i>	<i>High</i>
Daily dosage	40,000 to 1,000,000	
Total dosage	867,000 to 48,980,000	
Heparin sodium salt (milligrams)		
Total dosage	400 to 11,500	

COURSES OF PENICILLIN—HEPARIN THERAPY

Number of courses required in each case of the successfully treated group

<i>No of courses</i>	<i>No of Patients</i>
1	27
2	8
3	4
4	1
	—
	Total 40

dosage are easily gauged by the tilt-tube Lee White modification of Howell's method⁶ for determining blood coagulation time. A reading of 30 to 60 minutes is regarded as satisfactory evidence of an effectual anticoagulant level. Coagulation times above one hour are wasteful of the drug and may indeed be hazardous, particularly if the clotting time is prolonged to two or more hours. Effectually to heparinize the blood, necessitates subcutaneous deposits of 300 mg every second or third day or approximately 200 mg daily of the aqueous commercial product when incorporated in the venoclysis. Hyper-reactors require lesser amounts of heparin and hypo-reactors need additional dosage.

The estimation of penicillin dosage presents greater difficulty and requires the cooperation of the laboratory. Probatory sensitivity tests must be done on the offending organism. In general, the causative agents are inhibited within the dilutions of 0.007 to 5 Oxford units of penicillin per cc of test broth. Under these circumstances, the daily

dosage of penicillin (Table II) varies from 40,000 to 1,000,000 Oxford units, total individual unitage may range between the low of 867,000 and a high of 48,930,000 Oxford units. It may be observed parenthetically, as a tribute to the nontoxicity of the presently available preparations of penicillin, that the latter amount could be introduced without significant toxicologic phenomena.

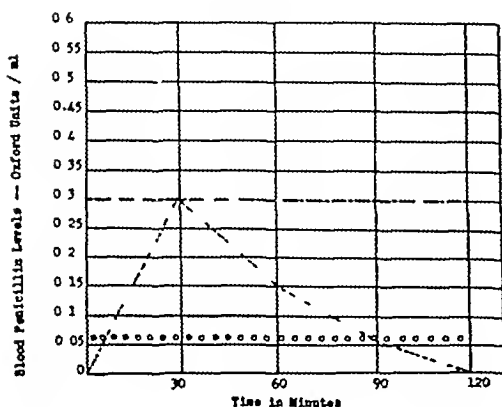
At the outset, through limitations in the supply of penicillin, an effort was made to reduce the span of treatment to an absolute minimum so that material might be available for as many patients as possible. Originally, a two week course of treatment was projected and was actually found adequate for the accomplishment of the disappearance of early endocardial lesions. Unfortunately, this two week course alone was insufficient for patients who had been ill for longer periods of time and a three week course was regarded as essential for those who had been ill for two to four months, a four week course was believed necessary for those who had had the disease for more than four months. It is our present opinion that our current practice of a five week course must be made the standard minimum when the supplies of penicillin justify treating the individual patient in optimum fashion. Additional courses are given whenever necessary and are well tolerated. Multiple courses are not uncommon in the advanced cases.

Based on penicillin-sensitivity tests, it appears that an average daily dose of at least 200,000 Oxford units is required. Increased dosage or a more prolonged span of treatment is necessary for patients who are deteriorated, or who show severe clinical manifestations of bacterial activity such as embolization, marked splenomegaly and violent temperature reactions. Additional factors that enter into the determination of the dosage level are the sensitivity of the offending organism to penicillin and the capacity of the patient to develop and maintain an adequate level of the anti-infective agent in the blood.⁷ To be therapeutically effective, penicillin blood levels must be far in excess of the *in vitro* bactericidal requirements, the best clinical results are achieved when the average unitage of penicillin is sufficient to develop and maintain a blood serum level of five to ten times the sensitivity figure. Inadequate dosage invites treatment failure and the organisms may acquire resistance that is so high as to render future therapeutic levels virtually unattainable. In at least one instance, we observed a forty-fold increase in the resistance of the organism to penicillin.

COMPARATIVE EFFECTIVENESS OF FRACTIONAL INTRAMUSCULAR PENICILLIN THERAPY VERSUS CONTINUOUS VENOCLYSIS

Total Daily Dosage = 240,000 Oxford Units

GRAPH I



KEY

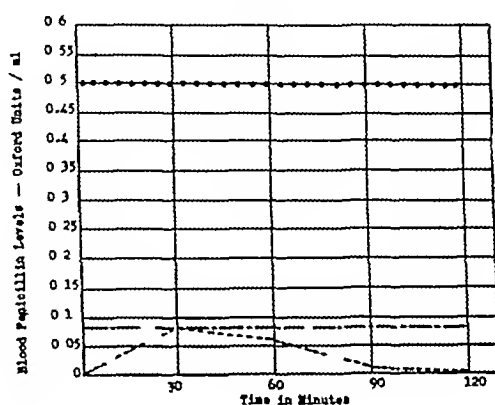
Patient A C #39, Successfully treated

000000 — Sensitivity of Organism

— — — Intravenous Penicillin Level

----- — Intramuscular Penicillin Level

GRAPH II



KEY

Patient S G #59, Refractory case.

000000 — Sensitivity of Organism

— — — Intravenous Penicillin Level

----- — Intramuscular Penicillin Level

GRAPH I—Patient A C—*Streptococcus viridans* inhibited by 0.06 O U per cc. test broth Daily continuous intravenous of 240,000 O U of penicillin achieved blood level of 0.3 per cc. of serum 20,000 O U given intramuscularly every two hours (totalling 240,000 O U per day) attained the intravenous blood level for only a small fraction of the treatment period During the latter part of the two hour period there was no detectable amount of penicillin in the blood serum This patient responded satisfactorily to one three week course of penicillin, 240,000 O U daily by continuous venoclysis with heparin in sufficient amounts to maintain coagulation time between 30 and 60 minutes

GRAPH II—Patient S G—*Streptococcus viridans* inhibited by 0.5 O U per cc. test broth (very resistant type) Neither continuous intravenous nor fractional intramuscular administration of penicillin in daily dosages of 240,000 O U achieved therapeutic levels It was impossible to attain satisfactory levels even when the penicillin was stepped up to 1,000,000 O U per day This case was extremely refractory to treatment.

THE TECHNIQUE OF TREATMENT

It is our custom to devote the first few days of therapy to the determination of penicillin levels following intramuscular and intravenous administration of the drug During this probatory period, heparin is withheld primarily to obviate any dislodgement of loosely attached vegetations

Our experiences indicate that intravenous injection of penicillin is decidedly the method of choice, intramuscular injections result in the attainment of a higher peak which cannot be maintained and which is

TABLE III
REACTIONS OCCURRING DURING THERAPY—SUMMARY

	<i>Chills and Fever</i>	<i>Fever</i>	<i>Local Pain</i>	<i>Regional Angitis</i>	<i>Regional Adenopathy</i>	<i>Urticaria</i>	<i>Vesicular Eruptions</i>
Penicillin Intravenous	Rare	Rare	O	Frequent	O	Occasional	Occasional
Penicillin Intramuscular	O	O	Common, degree Variable	O	Occasional	O	O
Heparin Subcutaneous	O	Common	Common, degree Variable	O	Occasional	O	O
Heparin Intravenous	O	Common	O	O	O	O	O
Penicillin and Heparin Combined	Not Uncommon*	Common	Uncommon	Occasional	Uncommon	Occasional	Occasional

* Causative factor(s) not clear

followed by a prompt and abrupt decline so that, for a sizable fraction of the treatment day, the blood is virtually free of detectable amounts of penicillin (Graph I, II) In contrast, the intravenous injection produces a constant and sustained level Only rarely, when the patient is in congestive failure so that the additional intravenous administration of the bulk of fluid seems more than the circulation can maintain, do we resort to intramuscular introduction, at the earliest possible moment then, we revert to the continuous intravenous drip employing minimum amounts of diluent In all instances, when available, Ringer's solution is employed as the vehicle, the patient is placed on a salt-poor intake and heparin is deposited subcutaneously as soon as the preliminary steps have been completed

Accessory therapeutic measures include the use of high caloric, high vitamin diets, supplementary multivitamin preparations, the use of hematinics in liberal dosage where there is anemia and the resort to frequent transfusions when indicated The latter require temporary

interruption of heparinization and hence are postponed, if possible, till the termination of treatment

TOXICITY

Reactions to treatment (Table III) occur frequently. Those of minor importance include chills, fever, local pain, regional angitis, regional adenopathy, urticaria and vesicular eruptions.

Febrile reactions are rather common and may be ascribed to a variety of factors. There are the obvious pyrogenic factors such as airborne contaminants. This is controlled by using sterisol bottles and periodic refrigeration. The substitution of viscose instead of rubber tubing eliminates a small fraction of reactions but does not justify its universal use. The incidence of troublesome regional angitis with its attendant rigors and sharp rises in temperature can be reduced by changing veins and apparatus every 3-4 days. Wherever possible a vein about the wrist or forearm is used to allow freedom of movement.

Thrombophlebitis seldom occurred in our heparinized patients even when this was a troublesome complication of the early penicillin era. Elaborate immunologic tests done with early crude and progressively purer products of penicillin have failed to elicit any instance of allergy in any of our patients despite multiple courses of intensive and extensive therapy.

Febrile reactions due to heparin are frequent, for the most part due to excessive anticoagulant activity. These are overcome readily by the mere withdrawal of the drug. One patient under combined penicillin-heparin therapy developed clinical manifestations of sensitivity to heparin. Attempts to resume the conjoint therapy were followed by episodes of chills and fever, the last one being associated with generalized urticaria. Intracutaneous tests were negative to penicillin but gave a moderate reaction to heparin. He has since received as much as 1,000,000 Oxford units of penicillin daily intravenously for some weeks without untoward reactions.

Urticaria has, at times, been troublesome, mostly post-therapy, and is almost invariably attributable to penicillin.

RESULTS OF THERAPY

The results of therapy (Table IV) of subacute bacterial endocarditis, using the combination of the intravenous introduction of the

TABLE IV

RESULTS WITH PENICILLIN-HEPARIN IN SUBACUTE BACTERIAL
ENDOCARDITIS

Total No of Cases (Consecutive and Unselected)		54	100%
Duration of illness prior to Penicillin-Heparin Therapy (Weeks)	1 to 78		
Penicillin sensitivity of causative organisms (Oxford Units)	0.007 to 0.5		
No of cases in which therapy was successful		40	74%
Patients Living	87		
Patients Deceased—Other Causes	8		
Post-Therapy Period of Observation (months)	2 to 15		
No of cases in which therapy failed		14	26%

TABLE V

ANALYSIS OF FACTORS IN FAILURES OF PENICILLIN-HEPARIN
THERAPY—SUMMARY

	No of Cases	Percentage
1 Patient Factors		
a. Cardiac failure	4	28.5
b. Cerebral embolism	8	21.4
c. Inanition	1	7.2
d. Intercurrent infection	2	14.3
2 Organism-Resistant	8	21.4
3 Reinfection	1	7.2
Total	14	100.0

anti-infective agent and mostly subcutaneous implants of the anticoagulant, have been tabulated according to the records of 54 consecutive and unselected patients. Many of our patients were in pitiful condition when therapy was inaugurated. In certain instances, congestive failure had reduced them to the point where any form of therapy was associated with considerable hazard. Other patients were in the ulcerative phase of the endocardial disease and were throwing off emboli from

friable and necrotic vegetations. Despite the precarious manifestations of many of the afflicted, we had no choice other than to inaugurate therapy, since refusal was tantamount to the imposition of a death sentence. Had we chosen to treat only those patients in the earlier stages of the disease and to eliminate those with manifestations of circulatory failure, ulcerative lesions, and embolic complications, a considerably higher incidence of favorable accomplishment might have been recorded.

As the records now stand, 54 patients were treated by combination of anti-infective, anticoagulant therapy. The duration of illness prior to treatment varied from one to seventy-eight weeks, the penicillin sensitivity of the etiological organism varied from 0.007 to 0.5 Oxford units, sensitive to resistant. Fourteen, or 26 per cent of the group are recorded as failures, 40, or 74 per cent may be regarded as satisfactory results. In the latter group, 37 of the 40 are alive and many have resumed useful occupations, 3 have died of other causes. In the group of treatment failures, there have been 13 deaths from progressive circulatory failure, coronary occlusion, embolization and lobar pneumonia, or a total of 16 fatalities in the original roster of 54 cases.

TREATMENT FAILURE

Treatment failure may be attributed to patient factors, refractoriness of the organism or reinfection with the same or another strain of streptococcus.

Of the 14 treatment failures (Table V), it is our opinion that 10 might be attributed to inability of the patient to withstand the ravages of the infection and to utilize the full benefits of combined anti-infective, anticoagulant therapy. At least 4 of the patients suffered from circulatory failure, 3 encountered cerebral embolizations, 1 had profound inanition and 2 had intercurrent infections, notably, lobar pneumonia.

A second cause for treatment failure in 3 patients was the refractoriness of the organism. In unreported studies (Table VI) made by J. M. Sherman of Cornell University, an attempt was made to establish a correlation between streptococcus typing, penicillin sensitivity and the clinical response. In our series of 54 patients, Sherman worked with 13 different organisms and established the presence of three different species. Three patients, infected with a previously unidentified streptococcus, were resistant to therapy and all three succumbed. The

TABLE VI

VARIETY OF STREPTOCOCCUS AS A POSSIBLE INFLUENCE ON PROGNOSIS

Preliminary Report on Work in Progress
(Kindness of Prof J M Sherman, Cornell University)

<i>Causative Organism</i>	<i>No of Cases</i>	<i>Treatment Successful</i>	<i>Reinfection</i>	<i>Fatal Outcome</i>
<i>Streptococcus sp</i>	4	0	1	3
<i>Streptococcus mitis</i>	7	6	0	1
<i>Streptococcus bovis</i>	2	2*	0	0
Total	13	8	1	4

Streptococcus sp Apparently a new and distinct variety of streptococcus. Strains belonging to this variety show rather homogenous cultural and biochemical reactions

Streptococcus mitis The common throat viridans streptococcus

Streptococcus bovis Similar to so-called "Bargen streptococcus"

* One of these patients, N M—Case 32, subsequently died of heart failure. No evidence of bacterial activity at autopsy

blood of 7 patients disclosed a *Streptococcus mitis*, apparently more sensitive to penicillin since 6 of the 7 recovered and there was but one fatality, the remaining two victims were infected by *Streptococcus bovis* and one of these recovered while the other died. Significantly, the autopsy on the fatal *Streptococcus bovis* infection revealed evidences of a healed endocarditis.

The last treatment failure in a surviving patient is an instance of reinfection with another strain of streptococcus. Studies by J M Sherman indicate that the organisms recovered from the blood stream during the initial and subsequent attack are different. This suggests that the patient was cured of his disease, but not necessarily immunized to subsequent bacterial invasion. The original strain is *Streptococcus salivarius*, whereas the more recent strain is significantly the unidentified streptococcus found, as previously mentioned, only in patients who were resistant to therapy. It will be especially interesting to observe the response to the current course of treatment.



In the series of the 54 original patients, there were 16 deaths. Thirteen of the deaths occurred in the group of treatment failures as previously indicated, three of the fatal issues occurred in those who had been satisfactorily treated. The autopsies of two of the satisfactorily treated patients have afforded an interesting insight into the disputed problem of a temporary sterilization of the blood versus actual cure. Evidence in favor of actual cure is afforded by the descriptions of the heart valve as recorded in one instance by E. S. Maxwell of the Good Samaritan Hospital in Sterling, Kentucky, and in the other by J. W. Denton and A. F. Heyl of the New Rochelle Hospital.

Case—*N M (Graph III)*, age 29, female Subacute bacterial endocarditis, 12 weeks, *Streptococcus viridans* (penicillin sensitivity 0.031 O U) chronic rheumatic cardiovalvular disease, aortic, aphasic on admission due to cerebral embolus, responded well to one 23 day course of penicillin-heparin therapy, developed intractable congestive heart failure which resisted all therapy, blood stream sterile for more than six months until death Maxwell reports, in this case, that the right aortic cusp was almost completely destroyed and replaced by short fibrotic stubs A congenital aneurysm was present near the origin of the aorta It was Maxwell's opinion that death was due to cardiac failure

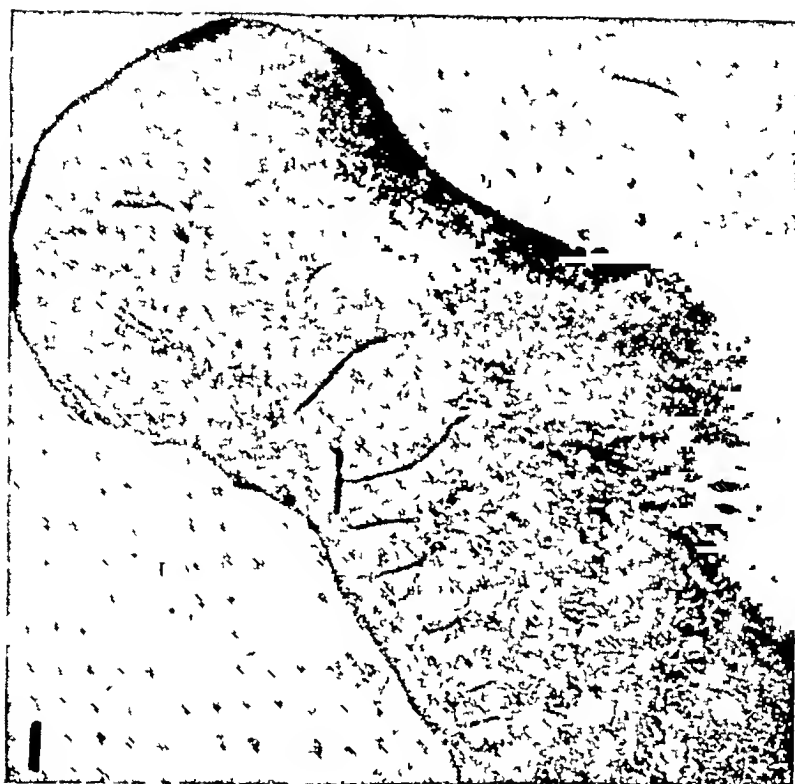
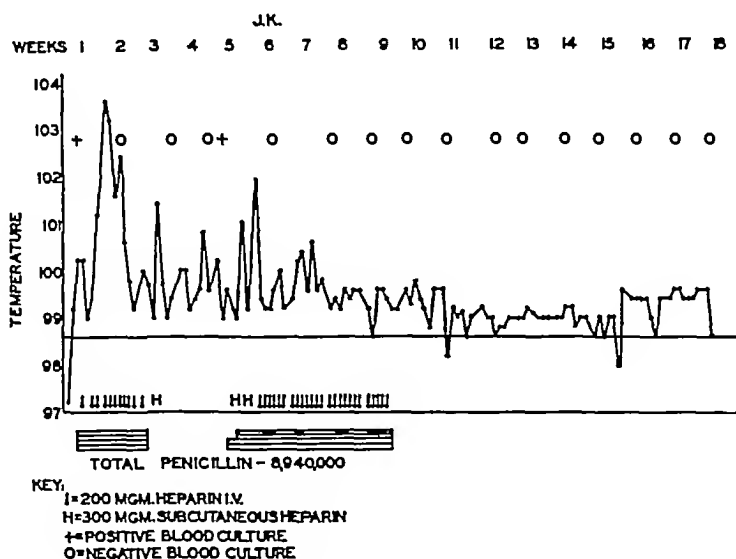


Fig 1—*Aortic Valve*—Note stump-shaped cusp which is fibrotic and completely endothelialized

Fig 2—*Stump of Aortic Cusp*—(Higher magnification) note that there is no evidence of active inflammation or any indication of bacterial activity



GRAPH IV

with marked visceral passive congestion. Histologic study showed fibrosis and hyalinization of the aortic stubs with no evidence of bacterial inflammation (Fig 1, 2)

Case—J K (Graph IV), age 33, female Subacute bacterial endocarditis, 28 weeks, *Streptococcus viridans*, chronic rheumatic cardio-valvular disease, aortic and mitral, two courses of penicillin-heparin therapy, 14 and 28 days respectively, discharged from hospital in mild congestive heart failure which progressed unfavorably, clinical behavior same as Case N M, blood stream sterile for more than three months until death. In this case autopsied by Denton and Heyl, they reported that there was a shredded, partially calcified anterior cusp of the aortic valve with marked insufficiency of the orifice. The heart was hypertrophied and dilated. There was severe chronic passive congestion of the viscera. It was the opinion of the pathologist that death was due to congestive heart failure and there were no histological evidences of active bacterial endocarditis (Fig 3, 4)

Interpretation of autopsy findings and the evaluation of gross pathological phenomena invite a discussion also of the significance of embolization occurring during the course of treatment. It is a well-established fact that embolization is a common complication of subacute bacterial endocarditis, but embolization has also been attributed to heparinization, particularly in the presence of thrombotic vegetations



Fig 3—*Aortic Valve*—Note the dense fibrotic character of the stroma and central fragmentation of the connective tissue. Note that the surfaces are completely endothelialized.

Fig 4—*Mitral Valve Nodule*—Note composition of moderately cellular fibrous tissue. There is no evidence of active inflammatory change.

TABLE VII

GROSS EMBOLIC INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

<i>Time Of Occurrence With Respect to Penicillin-Heparin Therapy</i>	<i>Number of Cases</i>	<i>Successfully Treated</i>	<i>Fatal Outcome</i>
Before treatment	4	4	3
During treatment	3		
After completion of treatment	1	1	
TOTAL	8	5	3

on the heart valves. To clarify this point, we have charted (Table VII) the relationship of embolization to therapy in eight of our patients. In four, embolic phenomena were present before the inauguration of treatment and four of these patients were successfully treated. Three patients in the first 30 of the series of 54 cases had embolization during treatment and succumbed. These are included among the treatment failures. It may be more than fortuitous that since introducing a probatory 3 day course of intramuscular penicillin treatment, there has been no intra-therapy cerebral embolization. In only one instance has there been a post-therapy embolization and that occurred in a patient who made a splendid recovery both from the infection and from the hemiplegia that resulted from the vascular occlusion. From these figures it would seem fair to conclude that pre-treatment embolization is not a contraindication to the inauguration of anticoagulant, anti-infective therapy and that embolization occurring during and following treatment is more likely a manifestation of the continued progress of the underlying disease than a result of the utilization of the anticoagulant.

SATISFACTORY RESULTS

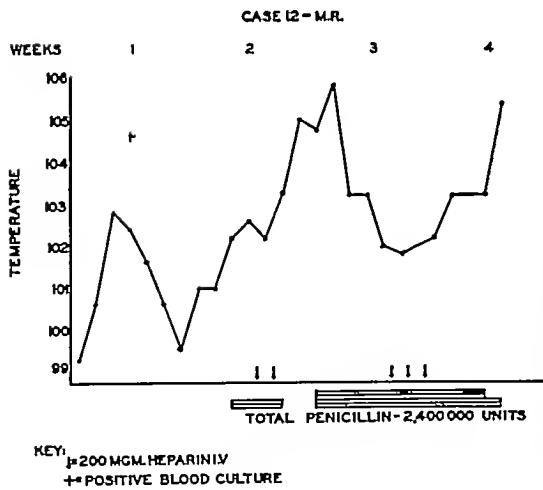
We have recorded 40 satisfactory results of whom 37 patients are still alive, many having resumed their normal activities. The most recent patient has been observed for only two months, but the oldest member of the group was discharged from the hospital fifteen months ago. In the favorable instance, the temperature falls to a normal level, the patient experiences a sense of well-being though, naturally, the mechanical deformities of the heart valves result in varying degrees of diminution in cardiac reserve. As in the instance of fatalities and treatment failures, the outcome of therapy is dependent upon patient and organism factors. Those patients who are seen soon after the onset of their bacteremia, who have relatively small vegetations, who do not suffer from ulcerative endocarditis or circulatory failure have the optimum chance for cure, provided that their infection is by a penicillin-sensitive organism. The second variable, so clearly delineated by Sherman's studies (Table VI), deals with the variety of infecting organisms. Apparently, infection with *Streptococcus mitis* or *bovis* carries a considerably more favorable prognosis than an invasion caused by the special streptococcus which is presently being subjected to searching inquiry by Sherman. The accomplishment of a favorable outcome in approximately



Figure 5



Figure 6



GRAPH V



Figure 7

Fig 5—*Aneurysm of Sinus of Valsalva* viewed from above. Note severe ulcerative lesion

Fig 6—*Aortic and Mitral Thrombo-Ulcerative Endocarditis* Note extensive myomalacia cordis, especially on cut surface.

Fig 7—*Myomalacia Cordis*—Gross fragmentation of the myocardium

3 out of every 4 patients leaves no doubt that the beneficial results observed in this unselected series cannot be attributed to spontaneous recovery. The severity of the manifestations of the disease in our group of patients precludes the possibility that we have been dealing with the bacteria-free stage of the subacute streptococcus endocarditis syndrome.

PROPHYLAXIS

Consistent with Libman's observation concerning the possible portal of entry in the upper respiratory passages and the teeth, we have included in our treatment program the elimination of foci of infection before permitting the patient to leave the hospital. To prevent a recurrence of exacerbation of the bacteremia, penicillin is administered parenterally and topically before and after the eradication of the focus.

It may be possible to illustrate the general principles which have been established through a concrete study of individual case records.

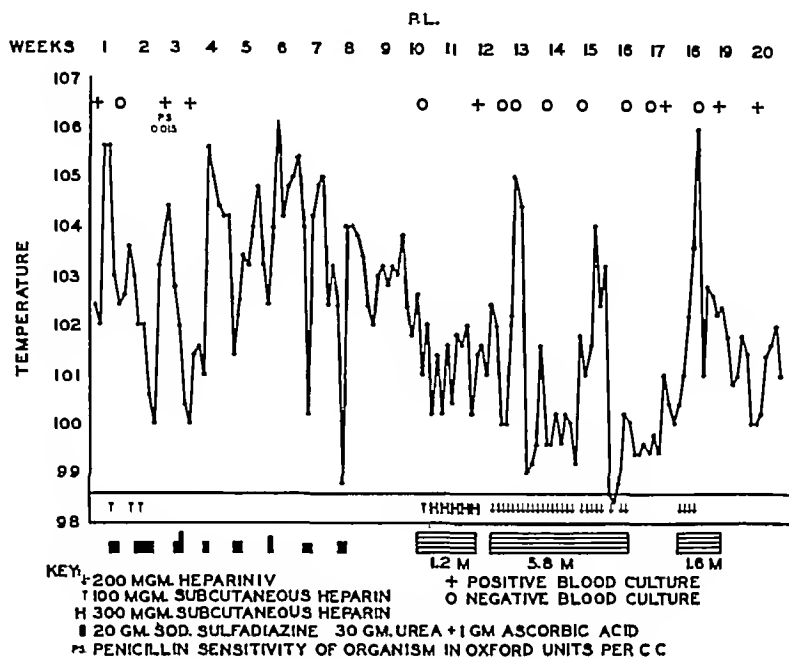
A ANALYSIS OF FAILURE

1 *Example of Therapeutic Failure due to Patient Factors*

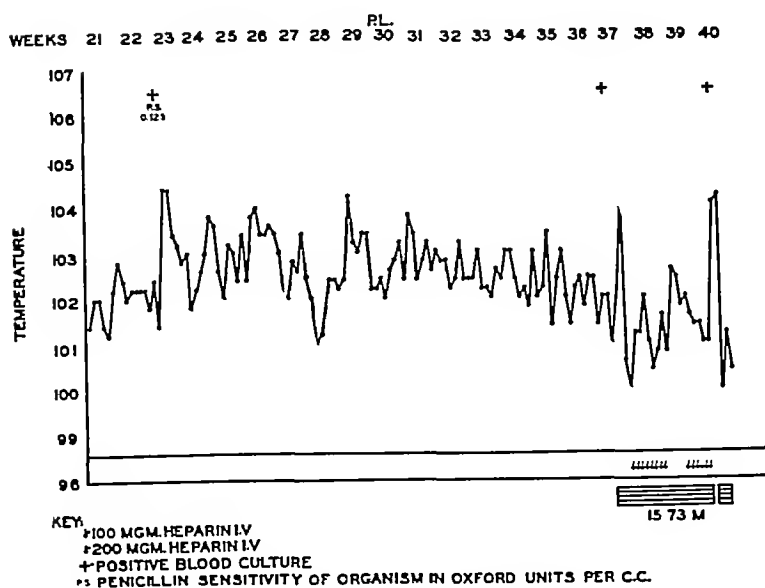
Case—M R (Graph V), age 47, male Subacute bacterial endocarditis, 6 weeks, *Streptococcus viridans*, chronic rheumatic cardiovalvular disease, aortic and mitral, discontinuous therapy for 12 days, severe myocardial embarrassment, pulmonary and cerebral embolization, progressive downhill course, death from circulatory failure (Fig 5, 6, 7)

2 *Example of Failure due to Organism Factor Infection with Streptococcus sp (Table VI)*

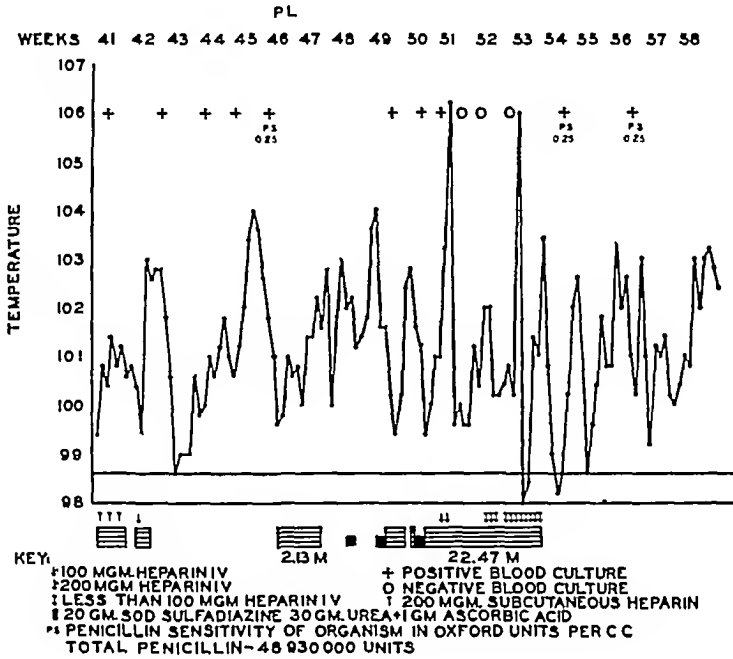
Case—P L (Graphs VI, VII, VIII), age 21, male Subacute bacterial endocarditis, 56 weeks, *Streptococcus viridans* (penicillin sensitivity 0.015 to 0.25 O.U.) chronic rheumatic cardiovalvular disease, aortic and mitral, three courses of penicillin-heparin therapy with but temporary improvement, treatment suspended October 31, 1943 for lack of material, resumed four months later with intensive massive medication, therapy interrupted because of extra-cardiac complications which caused death despite total of 48,930,000 Oxford units given in six courses, organisms recovered after successive courses displayed increasing resistance to penicillin as shown in laboratory assays and reflected by the lack of clinical response, confirmatory autopsy findings were "thrombo-ulcerative mitral and aortic endocarditis, with lesions



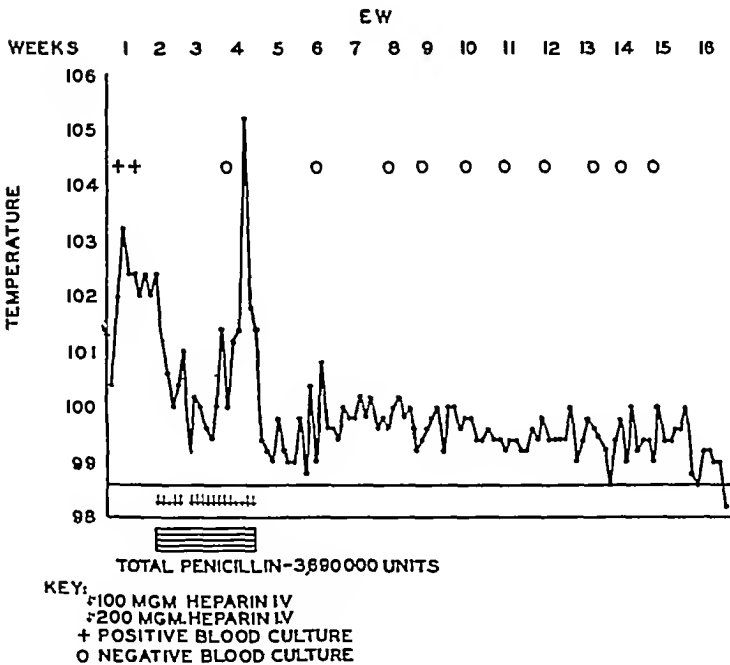
GRAPH VI



GRAPH VII



GRAPH VIII



GRAPH IX

predominantly aortic Valve stenotic and insufficient Chronic cardiac failure with accumulation of fluid in body cavities and passive congestion of viscera Death due to ruptured esophageal varices Long standing case with resistant organism"

B CO-EXISTENT RHEUMATIC VIRUS ACTIVITY

Penicillin treated patients are apparently susceptible to virus infections, due probably to disturbance of protective barriers by the drug Reactivation of rheumatic virus in successfully treated patients with subacute bacterial endocarditis may be explained on the same basis

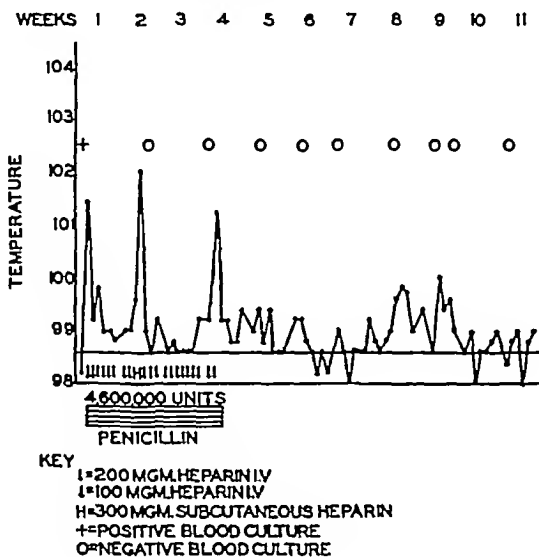
Case—E W (Graph IX), age 16, female Subacute bacterial endocarditis, 8 weeks, *Streptococcus viridans* (penicillin sensitivity 0.015 O U), chronic rheumatic cardiovalvular disease, aortic and mitral, one 17 day course of penicillin-heparin therapy sterilized blood stream, continued low grade temperature and elevated ESR, post-therapy, due to persistent rheumatic virus activity uncovered by successful therapy of S B E, confirmatory electrocardiographic findings of protracted rheumatic virus activity, culmination in severe rheumatic pericarditis with effusion six months post-therapy, development of hydro-pneumopericardium and its subsequent disappearance portrayed radiographically, despite all this no recurrence of bacterial endocarditis, blood stream sterile for over nine months, weight gain of 14 pounds, hemoglobin 82 per cent, ESR 40 mm/hr, continued active rheumatic suspect

It was an interesting observation to note that the rheumatic virus continued to operate despite the presence of sufficiently high penicillin levels to eliminate streptococcal *viridans* bacteriemia This and kindred observations tend to point up the recently reported experiences of the Army and Navy^{8,9} which attest to the resistance of rheumatic virus to anti-infective agents

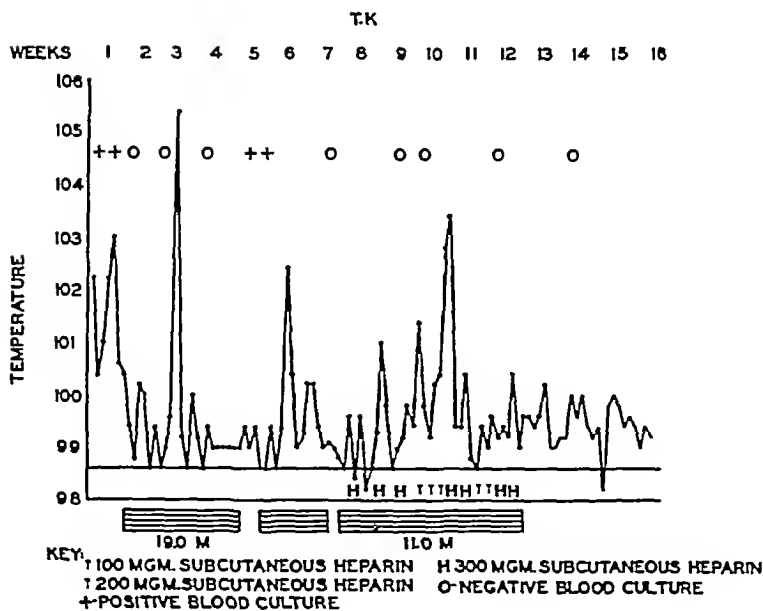
C FAILURE WITH PENICILLIN ALONE—SUCCESS WITH COMBINED PENICILLIN-HEPARIN Seven such instances to date

Case—F R (Graph X), age 43, female Subacute bacterial endocarditis, 12 months, *Streptococcus non-hemolyticus*, chronic rheumatic cardiovalvular disease, aortic and mitral, on fractional intramuscular penicillin therapy for 10 months totalling almost 9 million units with but transitory sterilization of blood stream, referred by M H Dawson and W Goldring for penicillin-heparin therapy, one course interrupted

CASE 6-FR.



GRAPH X



GRAPH XI

after 3 weeks because of apparent penicillin-heparin sensitivity, striking progressive clinical improvement, no clinical or laboratory evidence of bacterial activity for over 10 months despite complicating upper respiratory infection, prophylactic oral surgery

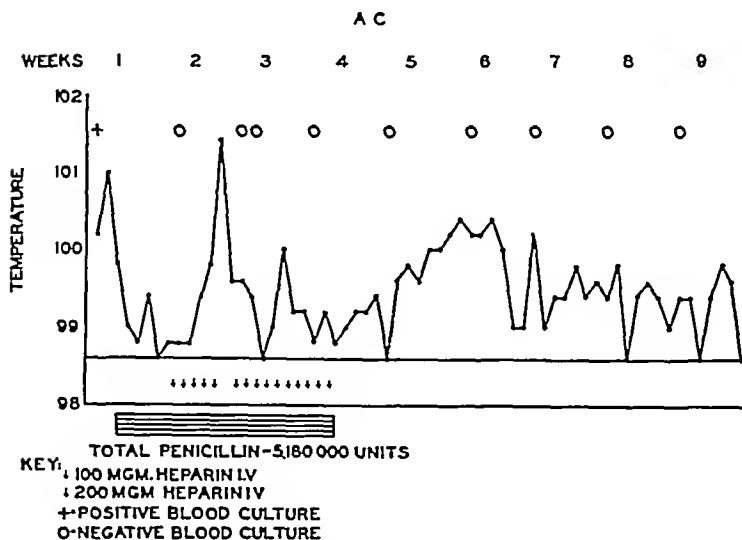
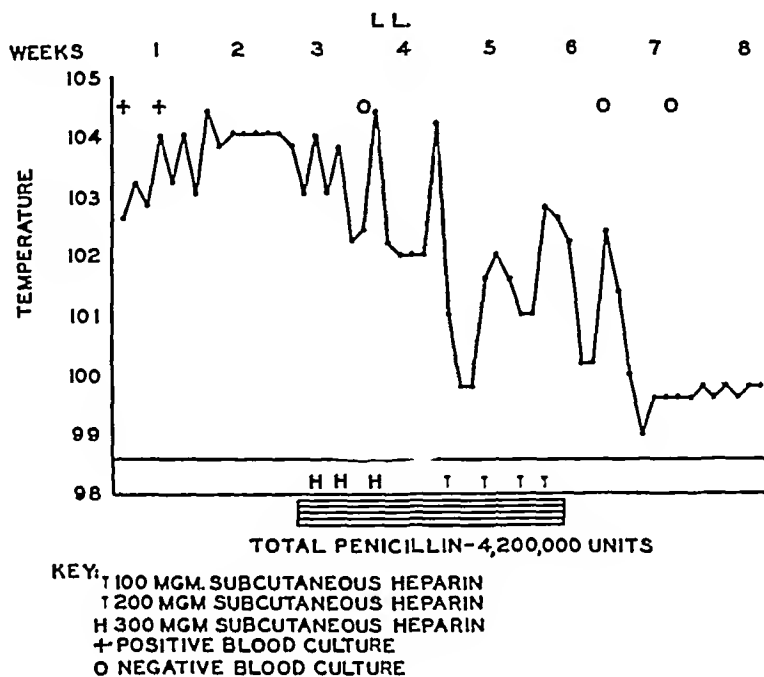
Case—T K (Graph XI), age 22, male Subacute bacterial endocarditis, 3 weeks, *Streptococcus viridans* (penicillin sensitivity 0.03 O U), congenital cardiac lesion, recovery from subacute bacterial endocarditis 2 years ago following sulfonamide-fever therapy, two courses of penicillin per se, totalling 19 million Oxford units ineffective for present reinfection, one five week course of penicillin-heparin, with lower dosage of penicillin, successful, no clinical or laboratory evidence of bacterial activity for over 2 months

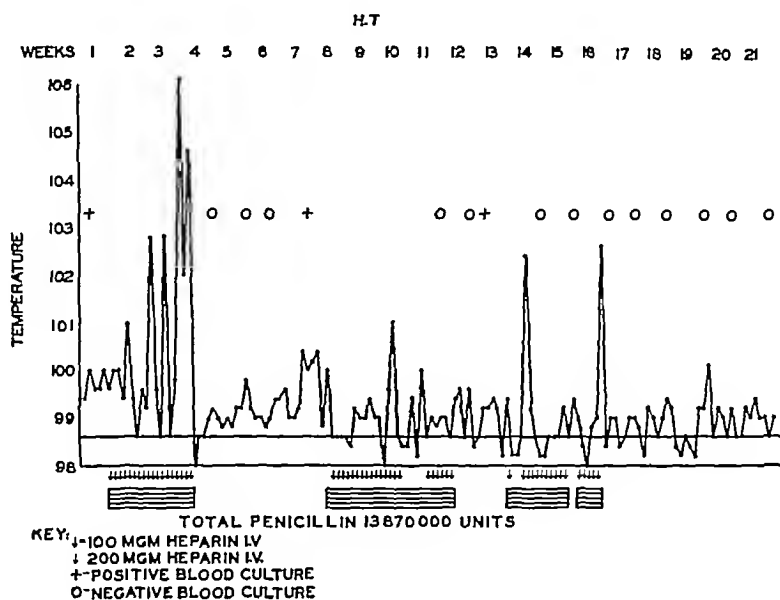
D COMPARATIVE RESPONSE OF PATIENTS TO THERAPY

Case—L L (Graph XII), age 33, female Mt Sinai Hospital (courtesy of B S Oppenheimer) Subacute bacterial endocarditis, eight weeks, *Streptococcus viridans* (penicillin sensitivity 0.03 O U), chronic rheumatic cardiovalvular disease, mitral stormy course characterized by rigors, spiking temperature, continuous intravenous medication impossible because of congestive heart failure necessitating dehydration measures, temperature immediately post-therapy ascribed to rheumatic virus activity, prompt response to salicylate therapy, infected dental foci removed, no clinical or laboratory evidence of bacterial activity for over 7 months, present weight 124 pounds, hemoglobin 80 per cent, ESR 7 mm/hr

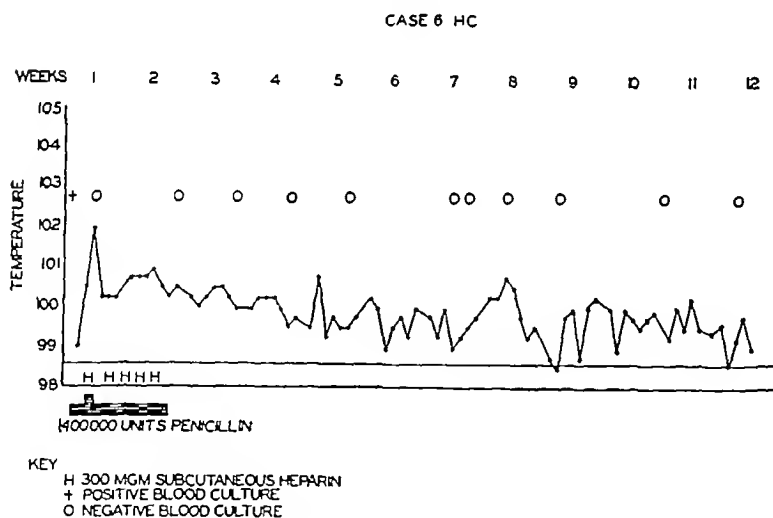
Case—A C (Graph XIII), age 59, male Subacute bacterial endocarditis, 3 weeks, *Streptococcus viridans* (penicillin sensitivity 0.06 O U) chronic rheumatic cardiovalvular disease, mitral therapy well tolerated, uneventful course apart from regional lymphangitis, no clinical or laboratory evidence of bacterial activity for over 5 months Prophylactic oral surgery

Case—H T (Graph XIV), age 27, male Subacute bacterial endocarditis, 24 weeks, *Streptococcus viridans* (penicillin sensitivity 0.06 O U) chronic rheumatic cardiovalvular disease, aortic and mitral, intensive sulfonamide therapy ineffective, admitted for penicillin-heparin therapy, advanced case, deteriorated, glomerulonephritis, hemoglobin 45 per cent, marked febrile response after 14 days therapy, widespread simultaneous embolization to brain, lungs, spleen and kidneys due ap-





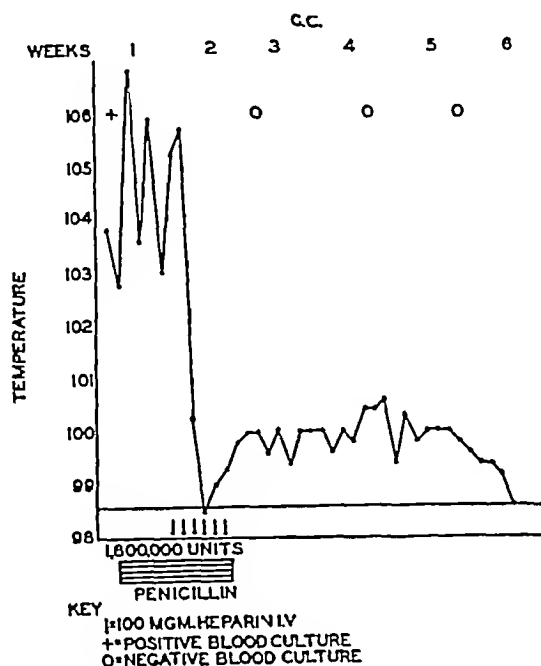
GRAPH XIV



GRAPH XV

bacterial activity for over 6 months, renal findings negative, prophylactic oral surgery, weight gain of 28 pounds, present hemoglobin 98 per cent, ESR 6 mm/hr

Case—H C (Graph XV), age 52, female (case # 6 of original series¹⁰), Subacute bacterial endocarditis, Streptococcus hemolyticus, 3 weeks, chronic rheumatic cardiovalvular disease, aortic, widespread, almost lethal embolizations, prompt, dramatic response to penicillin-heparin therapy, progressive clinical improvement and negative blood



GRAPH XVI

cultures, 14 months, present weight 163 pounds, hemoglobin 94 per cent, ESR 7 mm/hr. Has resumed work as a private secretary for past six months.

Case—G C (Graph XVI), age 10½, male Patient with Pneumococcus-type 33 endocarditis referred by Robert E. Gross of Boston and B. S. Denzer for sterilization of the blood stream prior to operation on a patent ductus arteriosus, ill with chills and fever for 3 weeks prior to admission, no response to sulfonamides, progressed favorably following a short course of therapy and was sent home clinically well, temperature chart shows graphically the spectacular response, hyperpyrexia attributed to overwhelming destruction of organisms and consequent liberation of bacterial proteins, when last seen over nine months post-therapy gained 23 pounds, hemoglobin 104 per cent and ESR 3 mm/hr.

CONCLUSIONS

A review of these illustrative cases permits of the following conclusions:

1. Age and sex have no bearing on the outcome of therapy.

2 The type of organism (apart from the so-called *Streptococcus* sp., Table VI) is immaterial to the outcome of therapy, provided it is inhibitable by penicillin within practical limits (0.007 to 0.25 Oxford units)

3 If the patient is in good physical condition, the duration of the disease less than three months, and the causative organism sensitive to penicillin, a satisfactory result may be anticipated, barring accidents, in virtually every case *

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* The invitation to address The New York Academy of Medicine during this Graduate Fortnight devoted to a study of the infectious diseases has been a source of tremendous personal satisfaction to me. I should be remiss, however, were I to conclude without expressing my thanks to my various colleagues and collaborators, among whom are included P. Rosenblatt, M. Lederer, H. J. Greene, M. D. Levin, M. Grolnick and E. Altire-Werber, Mr. M. Russell and Misses F. Kashdan and M. Koslof. I would like also to express my gratitude to Harold T. Hyman for his invaluable assistance in the correlation of my data for presentation.

PENICILLIN AND SULFONAMIDES IN THE TREATMENT OF OSTEOMYELITIS AND PYOGENIC ARTHRITIS*

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The introduction and availability, first of the sulfonamides and now of penicillin, justifies a consideration of the treatment of both acute and chronic pyogenic infections of bones and joints in the light of our present knowledge. This is because some of our previous views on this subject have been modified by the favorable results which we have observed in the use of these antibiotic agents. However it is realized that our knowledge is still incomplete and that future observations or the introduction of new antibiotic agents may modify the methods of treatment which will be described in this paper. It is also to be noted that this discussion is limited to infections in which the pyogenic staphylococci and streptococci are the offending organisms and these comprise the great majority of the cases in both civil and military practice.

Of the various sulfonamides now available sulfathiazole is the drug of choice in the treatment of osteomyelitis because it is more active against staphylococci than are the others and it is also effective against streptococci. Statistics indicate that in patients with osteomyelitis over two years of age staphylococci are the causative agent in over 90 per cent of the cases and in infants they are the causative agent in about 50 per cent. Almost all of the remainder are due to streptococci. Sulfadiazine and sulfamerazine have certain advantages in that they are better tolerated by some patients, but these drugs are not as effective as sulfathiazole in staphylococcal infections. Consequently, in this paper only sulfathiazole will be mentioned and it will be assumed that if this drug is not tolerated either sulfadiazine or sulfamerazine may be used.

In comparing sulfathiazole and penicillin we find that the latter is a more potent antibacterial agent against staphylococci and streptococci, it is effective against a wider variety of organisms, and its toxicity is so low that during its administration the possibility of toxic effects need not be considered. It has the disadvantage that it is not always available, it is expensive and it is not effective when taken by mouth, but must be administered intravenously or intramuscularly or applied locally. It is excreted rapidly and if effective concentration is to be maintained in the blood it should be given by continuous intravenous drip or by intravenous injections at two-hour intervals or by intramuscular injections at three-hour intervals.

Sulfathiazole has the disadvantage that it is not as powerful an antibacterial agent as penicillin and that toxic reactions are frequent and must be watched for while the drug is being taken. These can be minimized by maintaining a large fluid intake and administering thiamine chloride. It has the advantage that it is available, is relatively cheap and is effective when taken by mouth. It can also be used locally and as the sodium salt it can be used intravenously.

Both penicillin and sulfathiazole act directly on the bacteria and the drug must come in direct contact with the bacteria in order to exert its therapeutic effect. For this reason these drugs are most effective against organisms in the blood stream or in areas of cellulitis where there is an abundant circulation in close proximity to the bacteria. In such areas the drug can diffuse into the infected tissues and reach the bacteria in sufficient concentration to exert its effect. The drugs are relatively impotent against localized infections which are surrounded by avascular scar tissue or bone or by a zone of ischemia. In lesions of this type the maintenance of an adequate concentration of the drug in the blood stream will not sterilize the focus because the drug does not enter the focus in sufficient concentration to destroy the bacteria.

It is thus evident that they are especially useful in septicemia and in spreading infections in the soft tissues and bone, but frequently fail to cure or even to favorably affect the course of chronic infections which are well walled off and isolated from the blood stream. However, when the bacteria in chronic foci become active and break through the zone which walls them off and begin to invade the surrounding tissues these drugs may stop the spread of the infection and reduce the focus to its former chronic state. Both drugs are strongly bacterio-

static and even bactericidal when applied locally and for this reason local and systemic treatment should be combined when possible. Fortunately, penicillin and the sulfonamides are not antagonistic and may be used locally or systemically in combination or one drug may supplement or supercede the other without decreasing the effectiveness of either. Finally, occasional staphylococci are resistant to either or both sulfathiazole and penicillin.

TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS

This is an acute infectious disease which is characterized by a pyogenic focus in a bone and usually this is the most important lesion. There is a variable amount of involvement of the adjacent soft tissues and the bacteria may be present in the blood and metastatic foci may develop. Until it is proved otherwise, it may be assumed that the etiological agent in every case is a staphylococcus or a streptococcus and treatment should be instituted as early as possible on this basis without waiting until the etiology is proved by culture. Fortunately, with the exception of a specific antitoxin for staphylococcic toxemia, the measures at our disposal are effective against both organisms.

The disease varies greatly in severity. It may pursue a relatively mild course and even heal spontaneously without treatment or it may be fulminating in character and the patient may even die of the generalized infection before the local lesion in the bone can be diagnosed clinically. Fortunately, these cases of fulminating septicemia from an obscure focus in a bone are very rare. In the average case the patient is quite sick with high fever, mild septicemia and a definite and recognizable lesion in the involved bone. In the past the mortality was about 25 per cent and a large percentage of the survivors were afflicted with chronic osteomyelitis and the crippling which may result from this disease. By physiological treatment combined with local rest and carefully applied surgery we were able not only to reduce the mortality to about 10 per cent, but to lessen the incidence and severity of the sequelae of the acute disease.

With the advent of the sulfonamides we had, for the first time, an agent which, when administered systemically, was effective against the causative organisms. The more recent discovery and availability of penicillin places in our hands a safer and more powerful antibacterial agent. It is thus evident that our treatment must be revised. Even

before the discovery of the sulfonamides there was a definite trend towards less precipitate and radical surgery and more physiological care of the patient

Some observers considered acute osteomyelitis a systemic infection of which the local lesion in the bone was only an unimportant part and advised against surgery. I considered the focus in the bone the cause of the toxemia and septicemia and thought that this focus should be drained as early in the disease as the operation could be performed with safety, that is, as soon as the condition could be diagnosed and the patient could be gotten in suitable condition for the operation (Key^{1, 2, 3, 4}). It is not surprising that some observers now advocate chemotherapy alone and not only think that surgery is harmful (Baker, Schaubel and Kuhn⁵), but have also discontinued immobilization of the extremity (Hoyt, Davis and Van Buren⁶).

The objectives of treatment are to save the life of the patient, prevent spread of the local disease, clear the blood stream of bacteria, sterilize the focus in the bone, promote healing of the infected and damaged tissues and maintain or restore the health of the patient.

Since the effectiveness of penicillin and the sulfonamides varies directly with the ability of the blood stream to carry the drug to the bacteria, it is important that the treatment with these drugs be instituted as early in the disease as possible, even before the diagnosis can be made if the patient is seen that early. This is in order that the drug may reach the bacteria before extensive necrosis of bone and soft tissue occurs and they become separated from the blood stream by a wide and relatively impermeable zone of necrotic and inflammatory tissue. In a child with fever, localized tenderness, pain and loss of function in one extremity, acute hematogenous osteomyelitis or pyogenic arthritis should be suspected and the patient should be given a full dose of sulfathiazole immediately and hospitalized as soon as possible. The sulfathiazole should be continued until the symptoms subside or treatment with penicillin can be instituted or a diagnosis of some condition which is not amenable to this treatment is made. Localized joint or bone tenderness, muscle spasm, swelling, heat, redness and fluctuation confirm the diagnosis, but treatment should be instituted before these signs appear. This is not scientific medicine and will cause the drug to be administered to a few patients in whom it is not indicated but I believe that it will do little harm and may abort many

cases of osteomyelitis

Unfortunately, in the great majority of instances the nature of the disease is not suspected until the lesion in the bone is well advanced. When the patient is first seen by the surgeon or enters the hospital he has a high fever, is toxic and dehydrated and exhausted by pain and lack of sleep.

When this patient enters the hospital he should be given a sedative if necessary and subjected to a careful, but gentle physical examination in order to determine the nature, location and severity of his disease. Fluids should be given by mouth and physiological salt solution which contains 5 per cent glucose should be administered intravenously until the dehydration has been corrected. Blood should be taken for culture and for matching for transfusion. A white blood cell count, differential count, red blood cell count and estimation of the hemoglobin should be done and the urine examined.

If penicillin is immediately available a full dose (5,000 to 20,000 units) should be given intravenously or intramuscularly as soon after admission as possible and the intramuscular administration of from 2,000 to 15,000 units should be repeated every three hours until improvement is noted. Then the dose may be decreased. In some clinics the penicillin in amounts of from 60,000 to 100,000 units in 24 hours is given by continuous intravenous drip to very sick patients.

If penicillin is not immediately available, a full dose of sodium sulfathiazole should be given intravenously if the patient is very ill (5 to 30 grains) or sulfathiazole by mouth and its administration by mouth or intravenously if necessary in full doses every three hours should be continued until improvement or toxic manifestations justify a reduction in the dosage or until penicillin is substituted. While the patient is taking sulfonamides the urine should be examined daily and the urinary output maintained.

If facilities are available for determination of the level of the drug in the blood, this should be done and the dosage of sulfathiazole and fluid intake so balanced that a level of from 4 to 6 mgm per cent is maintained. But the fluid intake should not be restricted in order to raise the level of the drug in the blood. This may lead to increased toxicity from the infection and from the drug. Robertson⁷ gave from 4 to 9 grams of sulfathiazole daily to children and it is to be noted that children are more tolerant of the drug than are adults.

The affected limb should be immobilized in a large hot wet dressing with a splint or traction if necessary. This dressing should not be changed, except for examination of the part. Its principal functions are to relieve pain and immobilize the extremity. Frequent change of the hot wet dressing defeats both of these objectives. If it is covered with waterproof material the body heat of the patient will keep the dressing warm or hot water bags may be applied around it.

If the patient is anemic a small transfusion of from 100 to 250 cc of blood should be given and this should be repeated daily until the anemia is corrected. He should be given large amounts of vitamin B and C as long as the disease is active.

In some clinics (Baker⁵) staphylococcus antitoxin is given to combat the toxemia when this is indicated by a marked shift to the left in the differential count of the white blood cells. I have had little experience with this antitoxin, but believe that if properly used it is a valuable agent in the treatment of very ill patients who are toxic from staphylococcal infection. It must not be relied upon to cure the disease because it has no effect upon the bacteria, but merely tends to neutralize the toxins which they produce.

Of the above therapeutic measures, sedation, sulfathiazole or penicillin, immobilization of the part, intravenous fluids and transfusion, if necessary, should be instituted as soon as possible after admission to the hospital and the patient should then be left alone and permitted to rest.

It is noted that the x-ray is not mentioned. This is of no value in the early diagnosis of the disease and the patient should not be subjected to an x-ray examination until a week or more after the onset when sufficient time has elapsed for changes to occur in the bone which will be visible in the roentgenogram.

The question now arises as to whether or not surgery is indicated. In the past I have maintained that the focus in the bone should be drained as soon as the patient is ready for the operation, that is, after the above measures have been instituted and the dehydration has been corrected and he has rested and his general condition has improved to a point where the operation can be performed with relatively little risk. I now think that it is time to reconsider that opinion, because the principal reason for the operation was to relieve the tension in the bone and prevent or lessen the spread of the infection. We now have

sulfathiazole and penicillin which tend to limit the spread of the infection and gradually to lessen the tension in the bone. If treatment is started early it seems probable that these agents can sterilize the focus in the bone and so limit the necrosis of bone that gross sequestra will not form.

On the other hand, if the specific treatment is started relatively late in the disease (4 to 7 days after the onset) it is probable that the focus in the bone is so well established and so extensive that the drug cannot enter the abscess in sufficient concentration to kill the bacteria. Under these conditions it is still my opinion that the focus in the bone should be drained as soon as the patient is ready for the operation and the focus can be identified and approached surgically. In infants (under two years of age) the bones are so porous that operation on the bone is not necessary and the abscess in the soft tissue may be aspirated or drained by a small incision and usually the dead bone will be absorbed and replaced without sequestration. But in older children it is probable that intense chemotherapy or penicillin may cause the acute disease to subside and leave a chronic infected focus in the bone which may flare up when activity is resumed or at some later date. I have seen both of the above sequences of events occur in patients who had been treated elsewhere.

The operation may be done under general or local anesthesia and is a relatively simple and non-shocking procedure. The bone is exposed through the shortest and safest route and the periosteum split and two or more small drill holes are made through the cortex. A small window may then be removed from the cortex but no attempt is made to remove the infected cancellous bone or marrow. Hemostasis is effected, the wound is sprinkled with sulfathiazole powder and packed loosely with vaseline gauze and the extremity is immobilized in a well-padded plaster-of-Paris cast. If penicillin is available the vaseline gauze is put only around the margins and walls of the wound and a small catheter is placed in the depth of the wound and led out through the dressing and the cast and a small amount of penicillin (5 to 10 cc. of a solution containing 250 units per cc.) is instilled into the wound once or twice daily.

Immobilization is a very important part of the treatment and should be continued until the wound is almost healed or until chronic osteomyelitis is present and there is sufficient involucrum to prevent a patho-

logical fracture. The general supportive treatment should be continued as indicated until the improvement in the patient's general condition warrants a return to a normal regime.

It is to be emphasized that the operation is for drainage only and is a relatively mild procedure. When properly performed and rightly timed and followed by effective immobilization of the part, I do not believe that the drainage operation does any harm. I have seen patients in whom the disease appeared to spread widely through the bone and cause extreme destruction and involvement of the adjacent joints and even develop secondary foci while being treated with sulfathiazole. It is reasonable to think that early drainage of the focus in the bone would have lessened the spread of the disease in these patients.

When should the operation be performed? I see no reason for waiting until the temperature is normal and the acute infection has subsided. If the patient's general condition warrants the administration of a local or short general anesthetic (inhalation or pentothal) and the focus can be identified with a fair degree of certainty the focus should be drained. This operation is not performed as an emergency, but is done when the condition of the patient is satisfactory and at the convenience of the surgeon and the staff. In some patients it may be done on the day after admission or even on that day and others may enter the hospital with a severe septicemia and profound toxemia and may die of the infection or recover and the local disease subside without being fit subjects for a drainage operation at any time. If the disease is limited to cancellous bone sequestration may not occur, even in older children with severe infection.

It is possible that further experience with penicillin will cause this opinion to be revised, but I doubt it. When the disease is well advanced dead bone is present and, especially in older children, this will sequestrate and be difficult to sterilize by systemic treatment. The fact that the local and general symptoms have subsided does not mean that the patient is cured of osteomyelitis.

In pyogenic joints the situation is different and a sulfathiazole suspension or, better, penicillin can be injected directly into the joint cavity in sufficient amounts (10,000 to 40,000 units) to kill all susceptible bacteria in the joint and in the synovial tissues. If this is combined with adequate systemic treatment and is done before the cartilage is destroyed, the joint may be saved and a prompt restoration of func-

tion may be expected. The injection is made in sufficient normal salt solution to distend the joint cavity slightly and is repeated daily until the general and local symptoms subside. If the patient is seen late, after the cartilage is destroyed, the joint should be drained and then immobilized in a functional position and local and systemic administration of the drug continued just as was described for the infection in the bone.

Infected compound fractures should be treated roughly as described above, except that adequate drainage followed by reduction and immobilization are important parts of the treatment and the operation should be done as soon as the patient can be gotten in satisfactory condition. If gas bacillus infection is present the appropriate antitoxin may be combined with the penicillin or sulfathiazole and the operation should be performed as soon as possible and the involved muscles excised widely or the extremity amputated if it is devitalized.

THE TREATMENT OF CHRONIC OSTEOMYELITIS

In this condition surgery is usually necessary if the disease is to be cured, but sulfathiazole and penicillin are useful adjuncts to our surgery and are also useful in quieting down acute flare-ups of the chronic infection.

In a chronic osteomyelitis the disease may remain quiescent without drainage or other symptoms over a variable period and the focus may then become painful and acutely inflamed and an abscess may develop and rupture spontaneously unless it is drained. Or a sinus may close spontaneously and then pain, local inflammation and an abscess may develop. As a rule, these acute exacerbations of the disease are not accompanied by much fever, nor is the patient dangerously ill. However, this is not always true and they should not be taken too lightly, because sometimes the disease becomes invasive in character and may cause septicemia and even death.

In the past we have treated these acute exacerbations of the disease by rest in bed, forcing fluids and hot, wet packs and immobilization of the extremity and surgical drainage. Now, with sulfathiazole or penicillin added to the above measures, we frequently see the acute symptoms subside without abscess formation and the patient may again resume work within a relatively short time or he may elect to submit to an attempt to cure the disease by a radical surgical procedure. If abscesses form they should be drained as in the past.

In considering the surgical treatment of chronic osteomyelitis, the operation for cure should be undertaken only while the disease is relatively quiescent, that is, when fever, pain and local signs of acute inflammation are absent. Then, the patient should be hospitalized a day or two before the operation and penicillin or sulfathiazole administered in moderate doses (10,000 units of penicillin intramuscularly every 3 hours or 15 grains of sulfathiazole by mouth every 4 to 6 hours).

The operation should be performed just as carefully and thoroughly as though the drug were not being used and an attempt should be made to remove all sequestra and as much as possible of the dead and infected bone and to saucerize the cavities in the bone and eliminate the dead space. The infected walls of the sinuses are also excised. The wound is then sprinkled with sulfathiazole and sutured and the extremity is immobilized in a plaster-of-Paris cast. Dry penicillin powder may be mixed with the sulfathiazole powder or a small catheter may be placed in the bottom of the wound and the wound sutured around it and penicillin instilled into the wound daily for a week or so after the operation. The systemic administration of the drug is continued for from one to two weeks after the operation, or until the wound is healing. Depending upon the lesion, the cast is removed in from two to four weeks after the operation. Healing and probable cure can be obtained in about 60 per cent of the cases.

In those cases in which the operation fails in that the wound does not heal by primary intention after it is sutured, I have not found that the attempt to close it has precipitated a severe infection, but has resulted in a reduction of the size of the open wound and is followed by one or more sinuses which lead to infected bone. In other instances the wound will be healed when the cast is removed, but it will exhibit signs of infection or sinuses may develop when function is resumed, or at some later date. In these it will be found that the operation has been inadequate. The principal reasons for failure in my hands have been incomplete removal of sequestra, insufficient removal of dead or infected bone, inability to obliterate dead spaces, closure with too much tension and inability to close the wound because of damage to the soft tissues by previous surgery and long continued infection.

The use of adequate surgery within a few months after the subsidence of the acute disease would eliminate a considerable proportion of the severe cases of chronic osteomyelitis with large eburnated bone.

containing one or more large cavities and a variable number of small foci of disease. Such cases may be incurable by anything short of amputation and neither sulfathiazole nor penicillin can be expected to solve the problems which they present (Key⁸).

The dead bone should be removed as soon after the subsidence of the acute infection as it can be identified. It is wrong to wait for it to sequestrate or for a massive involucrum to form. The dead bone harbors infection and the massive involucrum becomes chronically infected as it is formed. Even if a pathological fracture is produced or follows the operation, this will do no great harm if the extremity is properly immobilized after the operation. Likewise, even if it is not possible to identify and remove all of the dead bone at the first operation something will be gained and a second or third operation may be performed if necessary. There is no reason why a surgeon should not plan to cure a chronic osteomyelitis by a series of operations, just as a plastic surgeon plans to replace extensive scar tissue by a series of skin grafts. The same is true of infected compound fractures. The surgeon should not wait for many months or years until the infection is almost incurable before attempting to create conditions favorable for elimination of the infection. The re-inforcement of good surgery by sulfathiazole or penicillin justifies a more aggressive attitude on the part of the surgeon in his war on infection in bone. On the other hand, he should do as little harm as possible and avoid the removal of living bone which may aid rather than interfere with healing. It is thus evident that subperiosteal resection is not recommended. Rather, one should perform a meticulous removal of as much dead and infected bone as possible.

From what has been written above it may be inferred that I no longer use or recommend the Orr treatment for chronic osteomyelitis. This is not the case. I both use and recommend it. It is used in wounds which cannot be closed satisfactorily and in wounds in which the infection for some reason seems too virulent to permit primary closure. This is especially true of extensive infections with large sequestra and foul-smelling, brown colored saprophytic pus. These foci are treated as adequately as possible, then sprinkled with sulfathiazole, packed loosely with vaseline gauze and immobilized in a plaster cast, or penicillin may be instilled through a catheter led out through the cast. They usually require one or more operations after the severe infection has subsided and may be closed or not, depending upon the state of

the wound at the end of the operation. The drug is also administered systemically both before and for a week or so after operation.

CONCLUSION

Acute and chronic osteomyelitis are surgical conditions in which sulfathiazole and penicillin are valuable adjuncts to, but rarely substitutes for sound surgical treatment.

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THE HISTOLOGY OF THE NORMAL AND DISEASED PANCREAS*

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THIS paper does not purport to be a complete review of all existing information on the subject indicated in the title. Since the structure of the pancreatic islets under normal and pathologic conditions is well covered in many textbooks of histology and pathology, in this presentation well known facts will be touched only superficially, and, instead, stress will be laid on some less generally known points, some of which are too recent to be included in textbooks.

The insular system consists of special cells distributed rather irregularly among the pancreatic acini and possessing a characteristic appearance and structure. Their shape is cuboidal, sometimes columnar or wedge-like. With most routine stains their cytoplasm is homogeneous and much lighter than that of the acinus cells because of the absence of both zymogen granules and chromidial substance. That is why larger accumulations of them can be recognized even under low power and with almost any staining technique. Although they can be distinguished from acinus cells by several cytological differences, their most distinctive feature is their specific granulation, demonstrable only with suitable differential stains. These granules set them off sharply from both the acinus and duct cells which are devoid of such granules.

Islet cells form well circumscribed, more or less bulky solid groups of a rather typical structure (islets) but are also found scattered singly or in poorly delimited small groups among the acini and in the lining of small ducts.

The islets can be studied as to number and size by various techniques such as supravital perfusion with neutral red or by planimetric measurement. This latter technique consists in projecting stained micro-

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scopic slides on a paper screen, outlining the islets, cutting them out with scissors, counting and weighing the pieces. In this way the number of the islets and their surface area in terms of percentage of the total surface can be calculated with ease. The important point is to take sections from many different parts of the gland since the distribution of the islets may vary considerably in different portions, although the notion that they are especially plentiful in the tail cannot be substantiated. There are data available concerning the number of islets in the normal human pancreas, and it seems that the range of variation is extremely wide. The total number of the islets in the human pancreas lies between 250,000 and 2,500,000, the majority of the cases being around 500,000. More meaningful is the total area of the islets, expressed in percentages of the total, since this figure includes both size and number of the islets and is actually proportional to the amount of islet tissue. The average normal value for man is 1 to 3.5 per cent. In certain animal species such as the dog and the cat the individual variation is so tremendous and the distribution of the islets in various parts of the gland so freakish that it is practically impossible to give normal values. Especially among dogs extremely low insular counts with almost complete absence of islets in some parts of the pancreas are quite common even under apparently normal conditions. Extreme caution is warranted before statements on changes in the amount of insular tissue, produced by experimental procedures, are made.

In size the individual human islets may range from a single cell to a group of over 300 micra in diameter, although the average islet will have a diameter of 70 to 150 micra.

The islets are composed of anastomosing short cords, usually only one or two cells thick. They are delimited more or less completely against the acinar parenchyma by the basement membranes of the acini and ducts or by the interacinar connective tissue. They do not have a capsule in the strict sense of the word and may be in direct contact with acini. Some islets are in direct continuity with ducts. A special kind of islets are the neuroinsular complexes which are composed of islets in intimate contact with sympathetic ganglion cells. They seem to be constant organites in the pancreases of all species. Nothing is known about their functional significance but the belief has been expressed that they may be chemoreceptors concerned with regulation of the secretion of insulin.

Extrainsular islet cells may be found scattered among the acini. Some of these tiny cell groups may be interpreted as slender peripheral processes of larger islets but individual islet cells, obviously outside of all insular relationship, are often seen wedged in between acinus cells. Other islet cells are embedded in the lining of ducts. These cells are likely to be completely overlooked if only routine stains are used but can be discovered easily in thin sections stained for specific granules. In certain animal species such as the white whale, extrainsular islet cells are very numerous, but they can be found in varying numbers in almost all species. In some human cases large numbers of them can be found both among the acini and in the lining of ducts, in other cases they seem to be completely absent. Unfortunately, quantitative data as to their occurrence under normal and under pathologic conditions are not available, although such data would be of great interest. A high count of extrainsular islet cells could explain such puzzling cases as that of Binger and Keith¹ in which no islets could be found in the pancreas at autopsy although there was no evidence of diabetes in vivo.

ACINUS-ISLET RELATIONSHIP

The relation between the islets and the acini has been a moot point ever since the discovery of the islets. All histologists agree that both acini and islets are formed from ducts. Also, there can be no doubt that islets are formed in embryonic life by the budding of acini. However, opinions are divided concerning the fixity of the two tissue types once fully developed. One group of workers finds no evidence for acino-insular transformation and asserts that both acini and islets are specific, noninterchangeable tissues which are capable of further growth or regeneration only by the division of their own cells, besides, of course, by new formation from ducts. Another, equally numerous group has maintained that the relation between islets and acini is dynamic rather than static and that conversion of acini into islets and vice versa does occur under functional stimuli even in the adult organism.

This divergence of opinions is due mainly to the application of too lax criteria to the diagnosis of acinoinsular transformation. Since at times it may be quite difficult to decide on the basis of routinely stained slides whether a particular cell is an acinus or an islet cell the subjective factor will become of decisive importance in settling the question. This is especially true in cases of regeneration and hypertrophy of the islets.

when the acinoinsular boundary may become more or less jumbled. Since the one positive means of identification of both acinus and islet cells is the demonstration of their specific granules, the only cogent evidence for acinoinsular transformation would be the finding, with specific stains, of cells containing both types of granules. If this criterion is accepted, the overwhelming majority of papers championing acinoinsular transformation must be dismissed because their authors failed to demonstrate such cells. The often observed apparent continuity between islets and acini, the lack of delimitation between the two tissues, are mere survivals of embryonic conditions and by no means an evidence for transformation. Being very much interested in the problem I have studied many hundreds of slides of both human and animal pancreases but have never seen a cell intermediate between an acinus and an islet cell either under normal or under pathologic conditions. I also paid attention to the often mentioned transitional forms between centro-acinar and islet cells, but the results were negative.

On the other hand, there can be no doubt that islets can be formed from ducts even during adult life. Although in the majority of human pancreases there is very little new formation of islets, in a number of cases all steps of such new formation can be traced. The epithelium of small ducts becomes multilayered, buds form which enlarge and finally become detached from the duct. In my collection I have several cases in which new formation of islets is quite conspicuous. Two of these cases show rather extensive arteriosclerotic changes with hyalinosis of the islets but both without any clinical signs of diabetes. Otherwise no correlation whatsoever could be found between the clinical pictures and the extent of regenerative changes as found at autopsy.

CELL TYPES

The first observations on the presence of more than one type of cell in the pancreatic islets date back almost fifty years^{2,3}. The foundations of the morphology and of the staining properties of the islet cells were laid down by Lane⁴ and Bensley⁵ about 35 years ago. They distinguished two cell types in the islet of the guinea pig: the alpha cells whose granules are alcohol insoluble but water soluble and the beta cells whose granules are alcohol soluble but insoluble in most aqueous fixatives. The staining technique used by Lane and Bensley was a rather complicated and capricious one which yielded good results only in the

guinea pig and was practically unusable in other species. A minimal change in the composition of the fixative produced color effects very different from those described by the authors, in fact, quite often a complete reversal of the staining reaction so that now the alpha cells stained as the betas should and vice versa. The same applies to a number of similar stains developed on the analogy of Lane's so-called neutral gentian. This inconsistency of results led to a considerable confusion, and it may be said that all papers based on the results of the Lane-Bensley staining technique are of somewhat doubtful value unless they come from the authors themselves or from their pupils who are thoroughly familiar with the knacks and pitfalls of the technique. The Mallory-Heidenhain stain if used on very fresh and properly fixed tissue gives a brilliant picture of the islets in practically all species. The alpha cells show ruby-red granules, the beta cells indistinct orange-grayish ones, and a third type of cells, Bloom's D cells,⁶ sky blue ones. Curiously, in the guinea pig the color effect of the alpha and beta cells is reversed in that the alpha cells are orange and the beta cells red.

The chromium hematoxylin-phloxin stain I described several years ago⁷ seems to be, on the basis of my own experience and of that of many other pathologists, a very reliable and easy stain that will differentiate with great clarity the dark blue staining beta cells from the red staining alpha cells. The D cells cannot be recognized as such with this stain because they stain very much like the alpha cells. The chromium hematoxylin-phloxin stain works equally well in all of the 20-odd species I examined, ranging from man to the pigeon and the frog. Almost any fixative will do, with the exception of alcohol, although with fixatives containing mercury salts certain corrective measures have to be taken before the staining technique can be applied with good success. The material need not be very fresh if one is not interested in fine cytologic details, very satisfactory counts can be done on tissues fixed as late as 6 to 8 hours, sometimes even 12 to 16 hours after death.

When these two stains, the Mallory azan and the chrome hematoxylin-phloxin stain, are applied to pancreases of the most varied species it is found that alpha and beta cells are invariably present in the islets of all of them. Although there are reports that the D cells are also a universal constituent of the islets of most species, I found easily stained clearcut specimens only in the pancreas of man and the guinea pig. Occasional bluish staining cells are seen in the islets of many

species but I am not quite sure whether they are actually analogous to the D cells of man and the guinea pig. There are absolutely no transitions between alpha and beta cells. On the other hand, the alpha and D cells do not seem to be two strictly different types since transitional forms are often seen. It is my impression that the D cells develop from the alpha cells through the aging of the latter. Besides these granular cells a number of agranular ones can be found in the pancreases of most species. The majority of these agranular cells are, no doubt, degranulated specimens of the three granular types.

In the islets of some species (guinea pig, dog) the different cell types are intermingled without any recognizable pattern, in others they tend to cluster together in a characteristic way. For instance, in the rat and the mouse the alpha cells occupy the periphery of the islets, while in the horse and in the cat, the center. In human islets the alpha cells often have a tendency to nestle against capillaries while the beta cells occupy the most avascular areas.

In most species the B cells greatly outnumber the alpha cells. Actual counts are available only on human and canine material. In normal human islets around 60 to 90 per cent of all cells are betas, 2 to 8 per cent are D-s, and the remainder alphas. Considerable individual variation in the differential count even between islets within the same slide is quite common. The extrainsular islet cells are mostly alphas.

Both in the human and in animal islets there is a considerable variability in regard to the extent and the degree to which the cells are granulated. However, islets of the same individual usually show the same degree of granulation or degranulation. Considerable degranulation, especially of the beta cells, is a common finding even under apparently normal conditions. Three types of degranulation are encountered in human material: (1) the diffuse, (2) the discontinuous degranulation, and (3) margination. Nothing is known about the importance and meaning of these various states of degranulation, although it is known that acutely high blood sugar levels tend to produce degranulation.

There is a large number of observations available on the effects of various acute and chronic stimuli on the islets. Most of these changes were studied with routine stains only or with the aid of the Lane-Bensley stains, and in many cases it is admitted that the results were very hard to interpret. The overwhelming majority of these observa-

tions are of doubtful scientific value owing either to lack of adequate controls or because the conclusions were based on impressions rather than on sound statistical evaluation of the data. I do not want to go into details of these reports but shall limit myself to the mentioning of a few well established facts. First, the administration of glucose causes an acute degranulation of the beta cells in the guinea pig.⁸ In the dog no such changes could be produced even with excessive doses of glucose. Partial ablation of the pancreas invariably, and ligation of the main duct often, cause hypertrophy of the islets. Starvation and pregnancy may also lead to considerable hypertrophy.

DIABETES

The literature on the changes of the islets in human diabetes was so thoroughly covered in Shields Warren's book⁹ and so well known to pathologists that I shall not go into details but shall bring out only some important points.

Although certain degenerative changes such as profound reduction in the amount of islet tissue, fibrosis, hyalinosis, lymphatic and hemorrhagic infiltration of the islets, along with certain cytologic alterations such as nuclear pyknosis and hydropic vacuolation can be considered rather typical of diabetes, there are a great many cases on record in which severe diabetes had been present in life, yet at autopsy the islets looked perfectly normal, in fact in some cases there were distinct signs of hyperplasia of the insular system. On the other hand, the pancreas may exhibit extensive degenerative changes quite typical of diabetes, without any *in vivo* disturbance of carbohydrate metabolism. The reasons of this puzzling inconsistency between the clinical and pathologic findings are so well given by Warren and Root¹⁰ that I shall quote from their paper verbatim.

"Whatever the cause may be, it seemingly acts over a long period of time, perhaps throughout the duration of the disease. The pathology which we find in the pancreas at autopsy rarely represents the initial damage to the organ, but rather the result of a long struggle between the regenerative activity of the pancreas and the degenerative changes caused by the diabetogenic factor. The pancreas is not a static organ like the brain or myocardium, unable to repair itself after injury.

"For some reason this static conception of the pancreas has become firmly established in spite of clinical and anatomical evidence to the

contrary, probably because the diabetic patient cannot be cured and frequently goes steadily downhill in spite of treatment. We believe that this unfavorable course of the disease is not due to failure of the pancreas to regenerate but to continued injurious action on the organ by the causal agent, eventually overcoming the regenerative efforts.

"A transient injury to the islands may explain the severe drop in sugar tolerance noted in diabetic patients during acute infections. The rapid reestablishment of the former level of sugar tolerance following recovery from the acute process may well represent the result of the rapid regeneration of the island cells."

To this I wish to add the following remark: the appearance of the clinical symptoms of diabetes depends only on the inability of the pancreas to supply a sufficient amount of insulin. We know from both experimental and clinical observations that the demand for insulin may vary tremendously under abnormal conditions. It seems that in experimental pituitary diabetes the pituitary extract acts mainly by reducing the efficiency of insulin in some unknown way, thereby increasing the demand. Clinically we have the so-called insulin-resistant cases of diabetes whose insulin requirement may be many times the amount calculated as normal for an adult individual. Even a perfectly normal pancreas may be unable to satisfy such demands. Therefore, all gradations between an absolutely incompetent insular system and a normal one that is relatively insufficient only in the face of excessive demand, are possible.

I hoped that the application of specific stains to diabetic pancreases may shed some additional light on the pathology of this disease. However, the results were disappointing. True, in some cases where the islets looked normal with routine stains, they proved to be very abnormal when stained for cell types in that the beta/alpha ratio was very low or beta cells were absent altogether. On the other hand, a great many cases gave a perfectly normal differential count. It is interesting to note that the beta cells may be well preserved even in greatly shrunken, hyaline islets. Summarizing the present status of the problem of the pancreatic pathology of diabetes, it may be said that although certain changes are highly suggestive of diabetes, it is impossible either to rule out or to confirm the diagnosis of diabetes with certainty on the basis of histologic findings.

The most important contribution to the pathology of diabetes has

been obtained from studies on various types of artificial diabetes. There are three types of induced diabetes known: the surgical, the pituitary and the chemical (alloxan) diabetes. The changes in surgical and pituitary diabetes consist of initial hyperplasia of the islets, followed by degranulation, vacuolation and ultimate disappearance of the beta cells, with fibrosis of the islets as the end stage. As to one of these changes, vacuolation, it should be remarked that it seems to be the expression of acute strain on carbohydrate metabolism. Conspicuous vacuolation may be seen in the pancreases of individuals who died with very high blood sugar levels. Within the last two years I had the opportunity to examine a fair number of biopsy specimens of pancreases. In three pancreases coming from individuals who had received very large amounts of glucose preoperatively vacuolation of the beta cells was a prominent feature. In both surgical and pituitary diabetes the alpha cells escape injury. The changes mentioned seem to be brought about by exhaustion of the insular tissue due to overwork. The proof for this theory is that both surgical and pituitary diabetes can be prevented if the islets are protected in the early stages of the disease by a low carbohydrate diet or by the administration of insulin. On the other hand, alloxan seems to kill the beta cells promptly, without any initial stimulation. Alloxan diabetes cannot be prevented either with a diet low in carbohydrate or by the administration of insulin. The pathologic changes are practically identical in all species.¹¹ Within a few hours after the injection of alloxan the beta cells become pyknotic. Later the cell cords become fragmented or coalesce into a homogenous debris in which individual cells cannot be recognized. In the course of the next two or three days the necrotic cells disappear without the slightest inflammatory reaction. They become replaced by proliferating alpha cells and by agranular cells only, the beta cells being completely gone. In the dog, the insular changes are accompanied by an extensive vacuolation of the epithelial lining of the small ducts, a change observed also in surgical and pituitary diabetes. This change may indicate that in the dog the duct cells are functionally related to the islets. There is no tendency to recovery from alloxan diabetes, except in rabbits. Rabbits whose diabetes shows improvement usually have a number of more or less normal beta cells preserved in their islets. These cells often show profound vacuolation, a picture similar to that seen in pituitary diabetes.

Finally, I wish to say a few words about islet cell tumors. Their

pathology was thoroughly covered by the excellent review of Duff and Murray,¹² here I want to call your attention to a few important points only. Not all islet cell tumors are functionally active, in fact only about 20 per cent of them are associated with attacks of hypoglycemia. There are over a hundred cases of functional islet cell tumors on record of which only 30 were studied by specific stains and out of this number adequately only 5 or 6. Owing to this small number of well studied cases it is impossible to tell whether functional tumors have a cellular composition different from that of nonfunctional ones. It would be very useful to establish a registry of islet tumors on the example of the Bone Tumor Registry for the purpose of making the comparative study of large numbers of islet tumors possible. On the basis of the few cases I had the opportunity to study, it would seem that although some of the functional tumors do contain cells more or less similar to the normal types, others consist only of cells that contain no identifiable granules.

COMMENT

According to all experimental and pathologic evidence, the beta cells are concerned in some important way with the regulation of carbohydrate metabolism. However, it is by no means proven, although probable, that they actually secrete insulin and that the beta granules are the morphologic expression of insulin content. In fact, insulin precipitated from commercial solutions by histologic fixatives does not show the staining properties of beta granules, furthermore, tumors with no demonstrable beta cells were found to have a high insulin activity. Therefore, the part played by the beta cells in carbohydrate metabolism is poorly understood. The function of the alpha cells is entirely in the dark.

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*Discussion by DR PAUL KLEMPERER, Pathologist, Mt Sinai
Hospital of papers presented by Dr Martin G Goldner and
Dr George Gomori*

I am sure I voice the sentiment of the audience if I express our gratitude for tonight's splendid presentations. The research on alloxan diabetes, stimulated by the original observations of the British authors, has been greatly advanced by the remarkable contributions of Drs Goldner and Gomori. Their painstaking cytologic studies have clarified the site of the cellular damage in the Islands of Langerhans, the complete necrosis of which had originally been reported by Dunn and his co-workers. With the discovery of the selective damage of the B cells by alloxan, their significance in the formation of insulin is now more firmly established than before. Beyond that, their investigations have demonstrated that the alteration of the B cells is not the result of overstimulation, as in the other forms of experimental diabetes, but the effect of direct injury by alloxan. This evidence, of course, must challenge our curiosity as to the possible mode of action of alloxan upon the B cells. Is there any answer or any suggestion to account for the destruction of these cells? I wonder if and how the action of alloxan can be inhibited. Is there any interference with enzymatic activity of these cells which could be demonstrated histologically? What is the effect of subtoxic doses of alloxan over a long period? The evidently constant absence of an inflammatory reaction in the vicinity of the damaged Islands of Langerhans seems to me a worthwhile problem although it might not be of particular significance to those primarily interested in

the diabetogenic action of alloxan. But from a general pathologic point of view, it is a provocative observation and I wonder whether our speakers could give us some of their ideas on this puzzling phenomenon. In line with this evidently well established feature of the alloxan pancreas, I should like to refer to the reports of Dunn and his co-workers who found a striking diminution and even absence of Islands in the late phases of alloxan administration. In some preparations which were shown to me by Dr. Wachstein, I had the same impression. Dr. Gomori did not mention such a disappearance of the Islands, and I wonder whether we were mistaken. Of course, the fact that the A cells are not affected by alloxan certainly makes it difficult to understand that the entire Island should disappear and it might well be possible that the small group of surviving A cells can be overlooked.

There seems to be a fundamental difference to the liver picture in A P E diabetes where the liver is devoid of fat except in those cases in which the A cells are also affected, as reported by Ham and Heist. I wonder if the speakers could enlighten us on this feature of A P E diabetes and, in particular, if they also found occasional A cell degranulation in A P E diabetes as seen by Ham and Heist. The absence of A cell damage in alloxan poisoning has been stressed by the speakers. It is, therefore, interesting to note that the liver of the experimental animals showed extensive fatty changes.

The constant sequence of hyperglycemia, hypoglycemia and permanent diabetes following alloxan administration has been one of the most puzzling phenomena. The conclusion arrived at by Drs. Goldner and Gomori as being the result of an action of alloxan upon the adrenals seems to me a brilliant explanation of the hitherto confusing issue.

Dr. Gomori has refrained from drawing any conclusion as to human diabetes from the investigations on alloxan diabetes. I understand his reluctance. Histologic examination of the pancreas, especially in reference to cytologic details, is very disappointing due to the interfering post-mortem changes. I believe that the principles which govern experimental diabetes also operate in human diabetes. But the demonstration of the mode of action by a correlation of the disturbed function with structural alteration which has given us so much insight in experimental diabetes, is unfortunately not so successful in human pathology. It is for this reason that we are usually frustrated if we are asked to explain diabetes by the demonstration of structural alterations. In

fact, we have no reliable histologic criteria for the pathologic diagnosis of diabetes. The hyalinization of the Islands of Langerhans is not found in the majority of cases and might be present without clinical evidence of diabetes. Parenthetically, I should like to ask Dr. Gomori whether he is in agreement with a recent paper by Aronheim who claims that the hyaline material is amyloid. As to extrapancreatic lesions in diabetes, I should like to remind you of the reports by Kimmelstiel and by Allen and Siegel from the laboratories of Mt. Sinai Hospital who found the characteristic intercapillary glomerulosclerosis in about 30 per cent of cases of diabetes. These findings are in my opinion valuable histologic criteria for the diagnosis of human diabetes. It might be worth while to study the kidneys in prolonged experimental diabetes of all types for similar findings.

In conclusion, I should like to say that the correlation of functional aberration with structural alteration has been one of the cornerstones of scientific medicine. If the dramatic discoveries of pure biological sciences have overshadowed the modest contributions of morphology to medicine in recent years, tonight's presentation of Drs. Goldner and Gomori proves that the old method of visualization if properly used is not an antiquated weapon in the arsenal of science.

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BULLETIN OF
THE NEW YORK ACADEMY
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MARCH 1945

SCIENTIFIC HUMANISM IN
THIS CHANGING WORLD *

Presidential Address

W W HERRICK

Y ou have seen fit to confer upon me an outstanding honor, the Presidency of The New York Academy of Medicine. To one who has devoted his years to the teaching and practice of his calling and to the perhaps too sedulous avoidance of executive duties and of office, your mandate brings with it a lively awareness of limitations, limitations of experience and, I fear, of capacity.

That this mantle, which has descended upon my shoulders from those of the medically distinguished of the past, be worn with no diminution of lustre, I bespeak your kindly tolerance and your generous cooperation.

I am bound to say, however, that I assume it and the attendant obligations in no shrinking spirit, but rather in that expressed by the phrase of Oliver Wendell Holmes "I am too much in earnest for either humility or vanity."

It has been said that an institution is but the lengthened shadow of a man. This, our Academy, is the almost century-long shadow of a few

medical leaders who, in 1847, first brought forward plans for its organization. This period in the history of our country has been called the time of decision, perhaps it also was such in medicine. In that year Virchow founded his *Archiv* and Pasteur graduated from the Ecole Normale. A Boston dentist had just brought to surgery the gift of anesthesia with the result that operations previously deemed impossible were undertaken. Valentine Mott, one of our founders, ligated the innominate artery, an unheard of surgical feat. Contributions such as that of Dr. Holmes on the Contagiousness of Puerperal Fever had given a new and stimulating aspect to medical problems. The negative contribution of Hahnemann made itself felt, as the public, ever ready to take the easier path, found the dilutions of Homeopathy certainly more agreeable and at times as efficacious as calomel and the lancet. The regular practitioners of the day felt the need to band together for mutual support and for the elevation of the standards of medical practice. Aware also of the ferment and progress about them, they declared it their further purpose to improve medical education and to contribute to medical literature. Shortly thereafter another primary purpose was added, the promotion of public health. As time has passed, the emphasis has gradually shifted to education, public health, and the dissemination of information on medical matters to the public.

Review of Academy programs uncovers a history of medicine since 1847. Papers describing the advances in surgical technique, the result of the use of anesthetics, occupy much of the earlier volumes. Studies in pathology, case reports, and matters of public health also may be found. With the work of Virchow the era of cellular pathology and of medicine based thereon is spread from the rostrum of this Academy. Here Charles L. Loomis and Edward Janeway, former Presidents, also Delafield and Prudden, among others of our fellowship, were pioneers in bringing pathologic anatomy into direct relation to bedside medicine. Austin Flint, an early President, brought physical diagnosis to its most finished stage. The next era, springing from the work of Pasteur, Koch, and Lister, was that of bacteriology. A president of this Academy protested against the seemingly too ready and widespread acceptance of bacteria in the causation of disease, and doubted if Pasteur had found a permanent place in medical science because of his polemical tendencies, nevertheless, progress in this phase of medicine continued, and the Academy played its part in making it public.

Later milestones in the widening scope of our profession may be considered the application of laboratory methods of chemistry and physics which have made clinical medicine much more precise and last of all the renewal of our faith in therapeutics crowned by the magical effects of the sulfonamides and of penicillin. There is no phase of these major steps in medical progress in which the Academy has not had its share and few indeed to which the Academy fellowship has not contributed.

Now we face a new era. The greatest war of all time must ere long come to a close bringing to our country and to our profession and to this Academy new obligations and new fields of labor. American medicine serves in every part of the world and everywhere it has met the challenge of great and compelling opportunity. It shall play its part in the reorganization of the world and may well be a great factor in the promotion of peace. To this end we must be assured that our own house is in order and our own capacity to serve remains unhampered.

In two years, the Academy will celebrate its centennial. It is not too early to begin to prepare for an occasion which should be notable in the medical progress not only of this city, but of the country. There are few medical organizations of equal importance that are more ancient. The Academy of Philadelphia is considerably older, having been founded in 1777. The American Medical Association is but one year our senior. At the 50th anniversary of the Academy, the then president of the United States made an address. In this, Grover Cleveland chided the medical profession because, in contrast to his boyhood days, the doctor of 1897 so seldom appeared in public life and so rarely held office. If at that time public office and medical practice were incompatible how much more so today when one considers the additions to knowledge which must be compassed by the physician. Not so much from choice as from necessity is it that the doctor avoids office. By training and tradition the problems of the individual absorb and concern him rather than the larger matters of public life. The doctor has not looked at politics. Politics, however, is beginning to look at the doctor. It is beginning to see in the field of medicine a new instrument of power with rich possibilities of a domination which may well affect seriously many long established practices of proven value. If the physician is to maintain that freedom of action which has given to our country an unequalled medical service it may be necessary for him to

follow the advice of Grover Cleveland and take a more active part in public affairs

Already the Academy has taken cognizance of this situation in the work of the Committee on Medicine and the Changing Order Physicians, publicists, social workers, laymen and holders of public office have met weekly for the discussion of every phase of this problem. The report of this committee will represent the most detailed and authoritative study of this complicated subject. It should be highly influential in securing appropriate legislation affecting the future practice of medicine in the United States.

Medicine has no small part to play in this changing order, it has the primary obligation of safeguarding the public health. Thus it can do best by the maintenance of its present high standards and by judicious action in any movement that threatens to lower those standards. Without abandoning its traditional practice of remaining aloof from politics, the Academy has the duty of bringing to bear the wise and expert counsel it commands. Certain social and political trends of the times have important biological implications. The experience of the profession in the practical aspects of sociology and of psychology, its intimate contact with the reactions of mankind to environmental changes of all sorts, gives weight to our opinions and judgments. It is proper that some of these be considered in no partisan spirit, but in a humble search for the truth.

There is a certain pessimistic philosophy abroad, not popular at any time, least of all in an election year, one in many of its aspects quite fallacious, yet with just enough validity to be arresting and with some relation to our problem. This philosophy* holds that the mass man has not changed since the Neanderthal days, that he remains motivated by what lies below rather than above the diaphragm, that he will always satisfy his needs by the minimum of effort, that, while capable of training, he is incapable of education because he has no wisdom and is, therefore, meat for the politician and the tyrant, that only rarely does a great soul rise above the mass, a Buddha, a Confucius, a Moses, a Plato, a Socrates, a Leonardo, a Shakespeare, a Washington, a Lincoln. The splendid list could be long. Obviously such a philosophy is vulnerable. We are not all either John Does or Emersons. There are

* Cram, Ralph Adams. Why We Do Not Behave Like Human Beings, in *Convictions and Controversies*.
Nock, J. A. The Memoirs of a Superfluous Man.

all gradations between The great leaders of medicine may not occupy the loftiest peaks with the major prophets, nevertheless, in their contributions to the welfare of mankind, Hippocrates, Vesalius, Sydenham, Virchow, Pasteur, Laennec, among the elect occupy comparable summits and give us, their humble followers, the right and the courage to speak when we sense any threat to the well-being of men or to our freedom to serve his needs

Industrialization and urban living have divorced man from nature, divorced him from that "universall and publick manuscript" of Thomas Browne, in which we learn certain fundamental realities, cause and effect, the value of leisurely evolutionary progress, the danger of abrupt and revolutionary changes, the worth of freedom The admitted evils of the industrial system have given rise to a demand for a new order It is proposed that the state assume responsibility for the security of the individual from the cradle to the grave Already we are embarked upon such a path, with little regard on the part of the mass man for the truism that security at the hands of the state and freedom as we have known and valued it are incompatible Freedom from want and fear makes a good slogan, but will it bear analysis? Short of that degree of privation which impairs initiative and energy, are not man's wants and man's fears the common motivating forces that arouse and compel action? To be sure there are higher motives—the love of service, the wish to rise equal to one's obligations, the pride in a good job—the last seemingly lost in the assembly line of modern industry These, alas, seem the motives of but a select few Even in the present crisis of our country in which the impetus to selfless, devoted labor in a common cause seems required of all, has the mass man, aside from the armed forces, shown any preponderant organized tendency to act on the higher levels? Can we, overnight, by some feat of political or social legerdemain, change this attitude or elevate these motives? Again, if all fear of privation be abolished by a paternalistic government, a fear about which the individual by his own efforts can do much, has there not been substituted a more menacing fear, a fear of the state, against which no effort of the individual can avail? Must we not estimate the effect upon the mind and spirit of the mass man of the removal of his wonted mainspring of action and of the deprivation of freedom which promises to result from the assumption by the state of this power over the individual? The trend of this statism seems toward the static order

of the ant hill or the bee hive Let those who would be drones remember that, in Nature, such are limited in number, in function, and in length of days As physicians we already have been concerned with and concerned about some of these effects upon the individual It is apparent that ere long we shall have to reckon with them as they affect our profession and, in consequence, the public health and welfare To these effects the Academy cannot be indifferent

I believe a possible result of what is called state medicine may well be a destruction of certain values of the spirit which are part of the very soul of our calling Let us consider some of these values "Scientific Humanism" has been declared a kind of religion, which is described further as the cult of the "sacredness of scientific progress in the promotion of the welfare of mankind" I know of no better definition of medicine than this Whatever other faith we may profess, if this be a religion, a "*Religio medici*," if you will, it is one to which all physicians of whatsoever time, race, or nationality subscribe No other body has achieved such universality, such catholicity, not the law, not the church Wherever physicians meet there is unanimity of motive, purpose, method, and this has been true at all times and among all peoples In this have we not set an example for the statesman and is there not here a value upon which the lawmaker should lay no ill-considered hand? Humanism has a twofold meaning on the one hand it implies a sympathetic approach to one's fellow man and his problems, a sense of his needs, his inspirations, and his aspirations, it practices faith, hope, and charity On the other hand humanism includes that which may be termed culture, a knowledge and appreciation of the stored wisdom and experience of man, as found in the "*Litterae Humaniores*" of our library, in not a few of the papers read from this rostrum, in the deliberations of our committees and in the programs of our Section on Cultural and Historical Medicine These are no mere overtones, adding only richness of quality to professional work, they are fundamental in the symphony Without science the physician is a menace, without humanism he is no physician If, perforce, the physician becomes a hireling of the state, his future dependent upon political favor, will not the humanistic side of medicine tend to shrink, perhaps even wither away?

For a moment let us be very practical Let us note certain concrete results A number of factors have contributed to the increased longevity

we now enjoy None, however, has approached in importance the public and private health work, in so much of which the Academy has been a leader, often, indeed, a pioneer Since the founding of this Academy, the life expectancy of man has increased from 35 to 63 years, that of woman from 38 to 68 years Can other learned callings show comparable results? In the last hundred years has the Law brought to the world more of Justice or made it easier to secure or less costly? Have legal clinics for the poor become numerous? Has Theology brought us nearer its noble goal of peace on earth, goodwill among men? Does this comparative record of medicine justify its being singled out for revolutionary methods of governmental control? Let those in other callings, whose freedom seems not as yet directly threatened, remember that encroachments by the state are progressive, that, if shackles are placed upon one group, they surely are being forged for the rest

Life has three prime and mutually dependent values without which all else is vanity They are the life blood of our calling and of our Academy They are truth, justice, and freedom If, as Emerson says, "truth is the summit, justice is its application to affairs," there are but two—truth and freedom

I like to think of this Academy as a Temple of Truth, not of the fixed dogma professing infallibility, but of a living truth that can change with the daily revelations of science, "a streaming fountain, if her waters flow not in a perpetual progression, they sicken into a muddy pool of conformity and tradition" Is not this the kind of truth that makes man or woman free, free to live a lengthened span, free to bear and rear with little pain or risk, free to build large cities and live in them without danger of epidemics, free to explore and live in any climate, free from smallpox, plague, yellow fever, diphtheria, and many other infections, free to live and to die with little pain? In the *Areopagitica* we read how "Truth indeed came once into the world with her divine master and was a perfect shape most glorious to look upon" and how Typhon, the god of evil, "took the virgin Truth, hewed her lovely form into a thousand pieces and scattered them to the 4 winds From that time ever since the sad friends of Truth, such as dare appear

went up and down gathering up limb by limb still as they could find them We have not yet found them all" It is our task to join these friends of Truth and gather up some of the fragments, in our library, in our committees, in the stated and section meetings, so that, although

it may not be given to us, those who shall come after may indeed see the lovely vision of the *Virgo Intacta*

The time calls for candid, honest and courageous leadership, a leadership based upon truth. If we of the Academy continue to give such leadership in our proper field, we shall have done all that is possible in preserving for our calling that freedom of action that has given American medicine its high standards and its effective service to the public.

This, our Academy, is a structure built by the wise and able leaders of our profession of this great city over nearly a century of effort. It is a heritage to be preserved with reverence. Let us dedicate ourselves to this work, this "Scientific Humanism" which, untrammelled, will continue to devote itself to the "sacredness of scientific progress in the promotion of human welfare."

ADDRESS OF THE RETIRING PRESIDENT*

ARTHUR F CHACE

Two years ago when I assumed the Presidency of The New York Academy of Medicine, I pledged myself to accept the challenge of the changing world and to endeavor to lead the Academy to ever greater heights of achievement in spite of the difficulties along the path, in a world torn by a devastating war. The magnitude of the problem served as a stimulus to our best effort, for as Browning so truly said—

“But a man’s reach should exceed his grasp

Or what’s a heaven for”

Tonight I shall speak of the past two years in terms of my stewardship and give you a brief picture of the progress made

The revolutionary forces in society are demanding adjustment of the public health agencies to the new order, with increasing intensity and the Academy is meeting these demands with ever-widening spheres of influence and constructive cooperation throughout its many departments

In spite of the insufficient stacks, the impossibility of procuring foreign periodicals and the difficulty in maintaining personnel, the Library has carried on with valiant and unbroken efficiency

In the past two years the Committee on Public Health Relations has maintained its tradition. The most important problems arising out of the war to which the Committee has given especial attention are: The progress of the treatment in Veterans’ Tuberculosis Hospitals, the taking part in the national inquiry into physical fitness, the need for which was shown by the high rates of rejection among the young men called for induction into the armed forces, the standardization of the training of WACS, so as to qualify them to meet the requirements of the A M A for various types of technician after their return to civil life. Among the long list of its activities the constructive recommendations improving the Workmen’s Compensation System in the State, the publication of Standards on convalescent care and rehabilitation and the book on

* Delivered at the Annual Meeting of The New York Academy of Medicine, January 4, 1945

Preventive Medicine, are most noteworthy

At the request of the Council, the Committee on Medical Education assumed charge of the installation of a permanent drug exhibit which serves two purposes the medical education of the physician in the newer pharmaceuticals and recognition of the contribution in research and accomplishment by the great pharmaceutical houses of this country More than 2,000 physicians viewed the exhibit during the Fortnight period and since then the daily attendance has averaged 62 persons The Committee has developed means to meet the expected post-war demand for post-graduate medical courses It is preparing for an extension of post-graduate courses in independent hospitals and is giving every assistance to physicians seeking such studies The Committee has maintained the high standards of its scientific programs with its Stated Meetings of the Academy, the Friday Afternoon Lectures, the Research Meetings and the Seventeenth Graduate Fortnight

In all the activities of the Committee on Information there is a common denominator which is the Academy's leadership and the Academy's service to those who are concerned with the education of the public in matters of health The Committee's projected Health Education Demonstration will have far reaching effect in guiding the in-service training of Health Educators Educators are evincing ever greater interest in the Lectures to the Laity In the past two years the publication of the two volumes of the March of Medicine has been enthusiastically received, as has the publication of the two volumes of the transactions of the Academy's Annual Health Education Conference The Committee has been called upon to review and help compose a very substantial number of manuscripts, which manuscripts, dealing with important health items, are published in magazines whose individual circulation runs into the millions The Academy, in this way, is exercising an influence which is nationwide and of major significance

In the early part of 1943 the Committee on Medicine and the Changing Order was initiated During the past two years it has gathered a vast amount of material and has thoroughly explored the field of social change It has gained the support of a very substantial number of citizens from every walk of life and in every major profession One of the twelve basic monographs which have grown out of these studies has already been published The others are in the process of preparation The publication of the monographs, essays and final reports will, we hope,

constitute a worthy contribution to the solution of the problem of the Changing Order

The improvement of the Academy's economic situation during the last four years has been a gratifying achievement which made possible an urgently necessary increase in the services of the Academy. In our effort to be of service to the official and voluntary health organizations we have loaned members of our executive force to the New York Tuberculosis Association, the Welfare Council, the Navy League and the Women's Army Corps. We are happy to announce that from three sources, financial support for traveling expenses and honoraria has been obtained. The Fortnight has been permanently endowed by the generosity of Mr. R. Thornton Wilson. The Academy has aided in the recruitment and training of practical nurses. The By-Laws have been amended for the strengthening and defining of the position of the Academy with regard to medical ethics.

The pattern of man's life falls into three domains. One in which he earns his livelihood, another in which he develops cultural pursuits and the third in which he labors without thought of reward in the service of mankind. The greatness of a nation can be measured by the amount of time and effort which its citizenry devotes to such a service.

During the past two years our Fellows, in addition to their contribution to the war effort, have given more freely of their time and energy to public health, educational and socio-economic interest, not alone in this community but in ever widening circles, which reach out to the state and country as a whole. With so many of our Fellows on active war service, it is significant that those who are carrying on the work at home are serving in greater numbers than ever before in committee work. This is forcibly brought to our notice in the Director's report, which shows that 389 Academy Fellows have served in over 203 meetings. Not alone has the routine work of the committees and sections been carried forward at an increased tempo, but in the new fields of endeavor which have been initiated, all the meetings have been fully attended.

It is a source of deepest gratification to me that in the years of my stewardship I should have received unfailing support and enthusiastic cooperation from every member of the Academy family. It has been a signal honor and privilege to work with the unselfish men and women in this organization which stands for all that is best in a noble profession.

The achievements which have been enumerated have been made possible through the wisdom and statesmanship of our Director, Doctor Herbert B. Wilcox. It has been a personal tribute to his wise administration, that our splendid staff has given so unstintingly of its assistance. Through his vision the Academy has steadily grown in prestige. It is fortunate, indeed, to have a man of such administrative capacity together with such kindness, human understanding and unprejudiced judgment.

The Academy is particularly fortunate in having as our next President, one of its Fellows who represents the highest traditions of the profession, who has had a wide experience as a clinician, diagnostician and educator and who is both a scholar and humanitarian. In following Doctor William Worthington Herrick's leadership in the years to come, I am sure that the Fellowship of the Academy will see it rise to even fuller achievement in the service of humanity.

THE TREATMENT OF BURNS AND WAR WOUNDS *

CAPTAIN L. KRAEER FERGUSON, (MC) USNR

U S Naval Hospital, St Albans Long Island New York

THE treatment of severe burns is a problem of importance in the surgical practice of civil life, but because of their frequency in warfare, they assume a place of major importance for those handling war casualties. During a six month period in the Solomon Campaign, 364 patients with burns were treated aboard a hospital ship, which represented about 10 per cent of the battle casualties. Burns were often associated with wounds and fractures, thus of 364 patients with burns, 103 had other injuries in addition.

Burns are frequently the cause of casualties in naval battles and operations. About 84 per cent of the burns we received arose from naval actions, and of the 1229 naval casualties we received every fourth patient had a burn. These were caused by bomb or shell flash, gasoline or oil fires on ships, less often by burning oil or gasoline on the water, powder explosions, escaping steam or boiling water and occasionally by electricity. Ashore, however, most of the burns were caused by the pernicious practice of using gasoline to light fires, and less often by bomb flash or other types of enemy action. In flyers, burns were the result of both aerial battles and plane crashes.

The various burning agents produce their own types of burns. Bomb and shell explosions cause an intense heat in a short-lived flash. All covered surfaces are protected, the face and hands being burned in nearly every case. In the face, where the skin is fairly thick, the flash causes vesication and destruction of the superficial epithelium. The thinner skin of the ears, eyelids and dorsum of the hands is often completely destroyed.

Gasoline and oil fires on ships and on land and water produce more widespread burns. Clothing often catches on fire, and as a result burns involve the full thickness of the skin or all but the papillary layer.

* Read October 17, 1944 at the Seventeenth Graduate Fortnight of The New York Academy of Medicine.

Scalds from escaping steam or water may involve any portion of the body, these produce a deep destruction of the skin but usually not of the papillary layer

Electrical burns destroy all of the skin layers and underlying tissue

SYSTEMIC DISTURBANCES IN PATIENTS WITH BURNS

In the treatment of severe burns, the problem is not only that of treating the burned area. The real problem is rather one of treating a patient whose physiologic processes have been markedly disturbed by a burn. This concept is fundamental because it turns attention from the relatively unimportant dressing of the burned area to the extremely serious and often fatal systemic alterations that occur with burns.

Shock Of these disturbances, shock is the first and most serious. It is believed to account for 60 to 75 per cent of the fatalities in burned patients and for practically all of the deaths that occur in the first two or three days after the burn is received. In our experience, its development and severity has depended more on the surface area involved than on the depth of the burn. Burns of certain parts of the body, as the face, abdomen and genitalia, perhaps produce shock more rapidly than burns of other areas.

The mechanism of the development of burn shock is a combination of factors acting in sequence. The first is a psychic one and it includes pain, fright, apprehension and frantic overexertion which goes with the production of the burn. In severe burns, especially where the burning continues over a period of time, as when clothes catch on fire or a survivor is surrounded by burning oil or gasoline on the water, this factor alone may be enough to cause fatal shock. It varies somewhat with the temperament of the patient. This type of shock is commonly classified as psychic or primary shock.

Secondary shock, which closely follows and even overlaps the phase of primary shock, is brought about by an increased capillary permeability resulting in a rapid loss of fluid from the circulation.

The increase in capillary permeability is the result of several factors. Of first importance is the effect of heat on the tissues. Kabat and Hedin¹ have shown experimentally that sensory impulses from the burned area play a role in the production of increased capillary permeability. As fluid loss leads to more marked hemoconcentration, oxygen transport is less efficient, and it is probable that anoxia brings about an

increase of capillary permeability in parts of the body away from the burned area

This fluid loss has been termed by Koch² "white hemorrhage" because it really is a loss of the blood volume by a seeping of blood plasma from the vessels into the tissues in the burn area. A relatively small amount of fluid is lost in blister fluid and on the burn surface. Most of the loss is into the tissues in and for some distance around the burn. The fluid loss begins at the time of the burn and increases progressively at an unbelievable rate. It is probable that most of the loss occurs in the first six hours, but it continues for at least 48 hours and probably longer. The amount of fluid lost may be amazing. Blalock³ has shown experimentally that it may equal 50 per cent of the blood volume in an animal with a burn involving half of the body surface.

Toxemia The period of shock, which may be considered to last for the first 3 or 4 days after the burn, gradually merges into a period of toxemia characterized by fever, albuminuria, hematuria and at times by delirium and vomiting. Absorption of toxic breakdown products of burned tissue, is held by some to be important in producing the symptoms of toxemia. In large part, however, it is due to infection. Since burns are primarily sterile by reason of the mode of causation, infection must be looked upon as secondary. It may arise as the result of contamination from the nose, throat or hands of attendant personnel, or from unsterile dressings or clothing. Infection may become apparent about the fourth or fifth day, and is a threat until complete healing of the burned area takes place. It is frequently the factor that produces additional destruction of the skin cells with consequent delayed healing. When bacterial invasion occurs, metastatic abscesses may appear in parts of the body distant from the burn, so that infection must be looked upon as a most serious complication and the one which most often produces fatalities in the later stages of the burn.

The toxic phase in severe burns is further complicated by the loss of the excretory function of the skin, renal insufficiency and a gradually increasing secondary anemia. As time goes on, the patient grows weaker and there is a loss of vascular tone leading to edema, thrombosis and embolism.

TREATMENT OF SYSTEMIC DISTURBANCES

A consideration of this brief summary of the physiologic changes

associated with severe burns leads logically to a plan of treatment designed to overcome or prevent them. The psychic shock at the time of the burn cannot be prevented, but the continued pain and apprehension may in large measure be relieved by adequate sedation with morphine given at the earliest opportunity. The Navy supplies morphine in syrettes, and usually an initial dose of $\frac{1}{2}$ grain was given. Subsequent doses of $\frac{1}{4}$ grain were given as needed.

Fluid loss may be partially prevented by the early application of pressure dressings. This principle, first suggested by Koch, has been of great value in our experience. In burns of the extremities, elastic bandages were applied over the definitive dressing on the burn area. In burns of the trunk, a scultetus binder was used to provide pressure.

There is some evidence that the use of adrenal cortical extract (eschatin) may reduce capillary permeability and so prevent fluid loss. In a few cases, we gave 5 to 10 cc doses intravenously every 6 hours for 2 to 3 days as suggested by Rhoads, Wolff and Lee.⁴ This may be an accessory agent of some value but should not be relied upon to prevent fluid loss in severe burns.

The most direct and effective means of overcoming fluid loss is by replacement with plasma. Plasma was available to us in adequate amounts in packages so that one unit of 250 cc corresponded to the plasma removed from 500 cc of blood. In estimating the amount of plasma needed we found the formula of Black⁵ most convenient and accurate enough for clinical use aboard ship when numbers of burns were being treated. His formula,

$$\begin{array}{rcl} \text{Hb after burn} & & 5000 \text{ cc} \\ \hline & = & \text{---} \\ \text{Hb before burn} & & 5000 \text{ cc} - X \end{array}$$

X = Plasma loss or plasma needed in cc

assumes that the hemoglobin after the burn bears the same relationship to the normal hemoglobin as the normal blood volume does to the blood volume after the loss of fluid caused by the burn. We assumed a normal hemoglobin of 95 per cent and solved the equation for various levels of hemoglobin, making the following table for convenient estimation of plasma dosage.

Hemoglobin	Plasma dose
95	250 cc (1 unit)
100	500 cc (2 units)
105	750 cc (3 units)
110	1000 cc (4 units)
115	1500 cc (6 units)
120	1750 cc (7 units)
125	2000 cc (8 units)
130	2250 cc (9 units)

Hemoglobin estimations were made every six hours during the first two days and we were thus able to follow the fluid needs of the patients fairly accurately and to give plasma as needed. Of course, if large amounts of fluids were taken by mouth, this method of estimation was not so accurate as at first, but it served as a reasonably useful and practicable clinical guide. Harkin's rule of giving 100 cc of plasma for every point above 45 in the hematocrit reading is not feasible aboard ships, because hematocrits are not usually available, and in treating burns in large numbers it is not practicable. Berkow's⁶ method of estimating the extent of the burn is helpful when a more accurate method is not at hand, but it is not too exact when plasma replacement must be done on this basis. In using this method, it is recommended that 1000 cc of plasma be given if 10 per cent of the body surface is burned, 2000 cc of plasma if 20 per cent is burned, and so forth, surface area estimates being trunk 38 per cent, lower extremities 39 per cent, upper extremities 18 per cent, and head 6 per cent.

It is important to have some way of estimating the plasma loss, because the tendency is to give too little rather than too much. In almost any severe burn, it is safe to give at least 500 cc of plasma (2 units) at once. We have given as much as 2,500 cc of plasma and 1,500 cc of saline in the first 23 hours after a burn.

The shock phase of burn therapy should not be passed without commenting upon the use and abuse of heat in this connection. Experimental evidence and clinical experience has shown that heat is no longer to be considered an effective means of treating shock. This is just as true in the care of burn shock as it is for traumatic shock. Overheating in a shock tent produces sweating and an unnecessary fluid loss in an already depleted patient. We tried to make the patients' environmental temper-

ature one of comfort, using covers or heat cradle as the case indicated, but making no effort to apply any additional external heat

Although infection is probably the most important factor in the toxemia of burns, its consideration may logically be held over until the discussion of the care of the burned area. Adequate fluid intake should be maintained, either by mouth or intravenously if vomiting occurs. Hemoglobin estimations usually show a rapidly developing anemia which demands repeated transfusions.

THE TREATMENT OF THE BURNED AREA

The care of the burned area should be considered of secondary importance except in so far as it helps in the prevention and treatment of the shock, toxemia and sepsis of the patient. Much can be done locally, however, to influence the systemic effect of the burn.

To begin with, those treating the burned patient should do everything possible to prevent contamination of the burned area. This means wearing masks and maintaining, as far as possible, a sterile technique in caring for burns. To avoid further shock, no attempt should be made to do any more than is absolutely necessary to clean up the burned area. Our practice was to remove loose bits of burned tissue and the raised surface of blebs and blisters as carefully as possible with scissors and forceps. As a prophylaxis against infection, a sulfonamide was used locally. We have preferred sulfathiazole in micro-crystalline form because it is absorbed more slowly and lasts longer (3 to 4 days) on the burned area. It may be sprayed on with an atomizer to cover large burned surfaces rapidly, or applied as a 3 to 5 per cent water-soluble ointment. Sterile gauze is then applied in generous layers and over this a firm pressure bandage. The elastic cotton webbing bandage does very well for this purpose, and it should be applied always to include the hand or foot distal to a burned extremity. To obtain even pressure on irregular surfaces such as the hand, sterile cotton waste was used underneath the bandage. In cases where burns were associated with wounds or fractures, plaster casts were often used as pressure dressings with good results.

Early dressings should be applied with the idea that no further dressings will be necessary until the burn is healed. Frequent dressing of burned areas accomplishes nothing except to open avenues for contamination to enter. Most second and superficial third-degree burns will

completely heal without infection in 10 to 14 days if the dressings are not disturbed. A leakage of serum through the dressing may call for a local re-enforcement but not a complete change of the primary dressing.

In third-degree burns with deep destruction of the skin but preservation of the papillary layer, the liquefaction necrosis of the destroyed skin is often mistaken for infection with pus when it appears on the dressings at about the end of the first week. The change of dressing is best delayed until the 10th to the 14th day, at which time much of the slough will have separated and can be removed by saline irrigations and mechanical removal with forceps and scissors. The burn is then redressed with sulfathiazole powder spray and pressure as before. This is repeated as necessary until healing occurs. Unless there is complete destruction of the skin, most burns will heal with this method of therapy without clinical evidence of infection. When there has been complete destruction of the skin layer, healing can occur only by the ingrowth of epithelium from the skin edges. This results in a prolonged period of painful dressings with much scarring and marked debility. Early skin grafting as soon as a suitable granulating base is apparent, permits rapid healing with a minimal scar, and it avoids the loss of weight and strength that otherwise occurs.

In the local care of burns, the objective to be achieved is a dressing that provides protection against contamination and against injury to surviving cells, a measure of bacteriostasis and pressure. It appeared to us that a dressing performed with sterile precaution, with the application of sulfathiazole and pressure, more nearly fulfilled these requirements than any other.

Tannic acid has been abandoned because it has been shown to destroy surviving cells, it sooner or later cracks and so permits infection to occur in the sloughing tissue, and it does not provide pressure except in circular burns where it may so constrict as to produce marked peripheral edema. Paraffin wax spray has the same faults except that it does not coagulate surviving cells. The triple-dye treatment is unsuitable in severe burns for the same reasons.

In severe burns patients occasionally lose weight and strength rapidly in spite of repeated transfusions and other supportive measures. This is often associated with a loss of vasomotor tone, thromboses and a gradually increasing debility and asthenia. We tried to counteract

these changes by getting patients out of bed early, at first letting them sit in a chair for a time and, as soon as possible, getting them up on their feet, this in spite of fever and toxemia. It seemed to us that this was worthwhile and we have seen no untoward reactions.

In 364 patients with burns, at least half of which could be classed as severe, we had one death due to burns alone. One patient died of multiple wounds, compound fractures of both bones of the lower leg and burns received in a plane crash. One other patient with multiple injuries and burns died soon after leaving the ship. It seemed to us that the death in these two latter cases was in large measure due to their other injuries. Most patients were comfortable within a few hours after their definitive dressing, and healing progressed rapidly. One patient with more than 75 per cent of his body surface burned by live steam recovered with only minor skin grafting.

THE CARE OF BATTLE WOUNDS

The incidence of wounds in battle varies a great deal with the type of military operation so the figures on war wounds vary from theater to theater. Our experience aboard a hospital ship gave the following statistics. In a six months period beginning with the amphibious landings at Guadalcanal and ending after the Japanese had been driven from that island, 6,807 patients were received aboard, of whom 3,333 were surgical casualties. (These figures represent only patients received aboard the ship from the battle area, but do not by any means represent the total casualties of the area.) The patients were divided 1,229 Navy, 1,589 Marines, and 509 Army, this representing a fair cross section of both naval and land casualties.

TYPES OF WOUNDS

The casualties arising from naval actions were usually produced by aerial bomb or naval shell fragments, or by injuries received from mine or torpedo explosions. About one in every four naval patients had burns. In land battles about half the casualties arose from bomb, shell, mortar or grenade fragments, and the other half from machine gun or rifle or pistol bullets.

Almost all wounds produced by explosion fragments were classified as shrapnel wounds. These varied in size from large wounds with much loss of tissue to small peppering wounds. They were usually multiple

and appeared in several areas of the body. In wounds from naval shells there was also a local burn caused by the red hot shell fragment.

Bullet wounds were more often single and often through and through. When the bullet passed through soft parts without encountering bone only a small tract of injury was made. When bone was struck, however, the deflection of the bullet caused a large wound of exit with a considerable tearing of soft tissues. There was a relatively large number of through and through wounds of the buttocks. These occurred due to the fact that the buttocks were often the highest point of the body as the soldier or marine crawled through the brush in land actions.

In the three thousand odd casualties, 2644 had open wounds, not counting the burns. By far the majority of the wounds were of the extremities, about 67 per cent. Wounds of the head and face 6.8 per cent, chest 7.4 per cent, abdomen 2 per cent. The latter figure does not give a true picture of the number of intraperitoneal injuries, however, because many wounds of the back, loin, buttocks and perineum caused intraperitoneal damage.

PRINCIPLES OF WOUND CARE

In anticipation of the handling of battle casualties, we had formulated some principles on which to base our treatment. Briefly these could be outlined, as follows:

- (a) Measures to control hemorrhage and to obtain hemostasis
- (b) The removal of dead, devitalized and contaminated tissue, and of foreign bodies. Under this head we had visualized the necessity of debridement.
- (c) The prevention of infection. Under this heading in addition to the mechanical removal of contaminated tissue, we had added the local and systemic use of the sulfonamides.
- (d) The avoidance of further injury. No antiseptics, gentle handling of tissues.
- (e) Physiological rest, by the use of immobilizing dressings, splints or casts.
- (f) Preservation of an adequate arterial circulation. Prevention of edema by elevation and pressure. Sympathetic block in cases of traumatic vascular spasm, the use of cold to reduce the local metabolism in cases of borderline vascular supply.

The care of wounds in warfare, however, requires some modifications of previously held ideas as to how to handle the injuries arising from trauma. There is no change in the principles of wound care, but there is required some thought as to how these principles are to be applied in view of new and strange conditions, varied facilities, multiplicity of injuries, numbers of casualties, and the necessity for moving the patients with a consequent succession of surgeons treating a wounded man.

Our first casualties came aboard seven days after they had been injured. Most of the patients had had little more than emergency treatment, which consisted of sulfanilamide or sulfathiazole powder in the wound and a battle dressing, many had had sulfathiazole or sulfadiazine by mouth. It was surprising to note the relatively low incidence of signs of inflammation in spite of extensive wounds. There was, of course, some sloughing due to the trauma of the injuring agent. It appeared to us that these cases were received too late for debridement, and, therefore, a conservative plan of treatment was decided upon. The patients were taken to the operating room. The doctor and two or three corpsmen scrubbed and dressed as for operation, and anesthesia was given (usually spinal anesthesia for lower extremity or lower abdominal wounds, and intravenous pentothal for other wounds that could not be handled by local anesthesia). The wound itself was protected by sterile gauze and a thorough mechanical scrubbing of the skin of the entire area was carried out, using large quantities of soap and water. After the skin surrounding the wound had been cleansed, the wound itself was exposed and thoroughly irrigated with saline solution. We had available sterilized enema cans, to the tubing of which a large sized catheter was attached and used as a nozzle. During the irrigation of the wound, such loose tissue as floated away in the irrigating solution was excised with scissors and forceps. We removed foreign bodies that were easily accessible in the wound and bone fragments which had no attachment to periosteum or muscle. An effort was made not to produce bleeding in this cleansing process, and no attempt was made to excise the wound or wound tissues. In cases in which a small wound was overlying a large, deep pocket, the incision was extended to make it correspond to the underlying wound. As experience was gained in the handling of these wounds, it was found that it was not necessary to remove caked sulfanilamide from an open wound as it came away with

the slough and necrosis or disappeared with time. In a few cases, it was necessary to partially remove the caked drug as it acted as a plug in the mouth of the wound.

After this conservative cleansing of the wound, microcrystalline sulfathiazole in the form of a powder was sprayed on superficial wounds, or it was introduced in an aqueous suspension in deeper wounds. In most wounds, a simple gauze dressing was applied with a considerable amount of pressure to prevent edema in the wound area or to disperse it if it was present. All large wounds of the extremities were immobilized with plaster splints or casts. When the patient was taken to the operating room, it was our purpose to give in that treatment and dressing the definite wound care. Unless it was necessary because of excessive secretions, the wounds were not dressed again during the patients' stay on the ship. Most of our patients left the ship before the end result of their treatment could be determined, but it was possible for us to follow these cases in the hospitals to which we had evacuated them and in a few instances we were privileged to carry the patients along until complete healing had occurred. This enabled us to evaluate somewhat our conservative form of therapy. It was evident that the wounds became clean and free of slough within a period of 10 days to 3 weeks after injury, and at that time it was found possible to perform a secondary suture in a large percentage of the cases. Even relatively large wounds could be completely closed if skin excision had not been carried out. In other cases, it was possible to close wounds partially by suture, reducing, therefore, by one-half or more the area which had to be covered by skin graft.

Such excellent results seemed to follow our regimen of mechanical cleansing, immobilization, pressure dressings and sulfathiazole locally in patients who came to us relatively late, that we were encouraged to follow the same regimen in early cases. It appeared to us that by the early local and systemic use of the sulfonamides there was little necessity for wound excision or extensive debridement.

We received aboard the ship numerous patients upon whom so-called debridement had been performed. This usually meant excision of the wounds with removal of all damaged tissue and loose bone fragments. The resulting wounds were much larger than the original wounds. No secondary suture was possible and frequently the convalescence and healing in these patients was prolonged.

No attempt at suture of battle wounds was made while patients were aboard our ship. However, we received a fairly large group of patients in whom suture had been attempted from the second to as late as the sixth day after injury. In tabulating these patients, we found that in 190 of these wounds sutures were successful, if one counts as successful wounds showing serum ooze, slight hematoma, and slight redness around the suture line. The majority of these wounds were small originally, less than 3 cm in length. We found that these wounds healed without suture in approximately 2 to 3 weeks. In 157 sutured wounds the entire wound had to be opened because of infection, hematoma, or necrosis. These usually were large wounds in which a debridement and suture had been attempted.

There were certain types of wounds, however, in which wound suture seemed practicable. Wounds of the face especially fell into this category. In our group, we had 35 facial wounds, of which 31 were successfully sutured. It is fortunate that wounds involving the face and mouth can be sutured successfully almost any time after their inception because these patients have not only to contend with the pain of the wound, but they have also a marked psychological disturbance because of fear of disfigurement, and in mouth wounds, they have marked dehydration and malnutrition due to the difficulty of eating and drinking. Some of our most grateful patients were those in whom suture of facial wounds was successful. Wounds of the scalp not involving the underlying bone or brain could also be sutured successfully in many cases. Eleven out of 16 scalp wounds healed primarily without infection even though they were sutured late. In our experience, wounds did poorly when they were associated with compound fractures in which suture and application of a cast had been performed. Some of our most severe infections appeared in such cases.

FOREIGN BODIES

Foreign bodies of all sizes and shapes were found, and they varied in number from 1 to 50. It was impossible to consider removal of all foreign bodies by operation, and it was found by experience that a great many of them could be picked out of the wound with forceps or hemostat without anesthesia. As the injured tissues became necrotic, foreign bodies frequently worked to the surface or could easily be reached through the wound.

Some indications had to be laid down for the removal of foreign bodies, and as experience grew these indications became more definite

1 Those which were easily accessible in the wounds were removed at the time of wound cleansing

2 Those which were superficial were removed by a simple skin incision

3 Those which, because of their size or position, caused interference with function, thus all foreign bodies in the joints were removed when possible Large foreign bodies in soft tissues were removed

4 Those which, because of position, caused pressure on vital structures, thus foreign bodies which pressed upon the trachea, upon the nerves, etc., were removed

5 Those which developed infection around them were removed, and in these cases the removal of the foreign body accompanied the incision and drainage of the infected area

6 Those which worried the patient because of their presence were removed

Patients were often upset by the knowledge that their tissues contained shell fragments in a certain area, and wished them to be removed The rule was that no foreign body should be removed in which the procedure of removal would cause more damage than the presence of the foreign body in the tissues Most of the foreign bodies could be removed under local anesthesia, relatively few of them showed any infection about them and in most cases after the application of sulfathiazole into the wound, the wound edges could be loosely brought together with 1 or 2 wire sutures

FRACTURES

Fractures occurred in 1,285 of 3,333 battle casualties More than one of every three patients had a fracture, and 46 per cent of the patients with wounds and contusions, or almost every other patient, had a fracture Fractures were observed in almost every bone of the body There were certain characteristics of fractures in military surgery that became apparent at once The fractures often involved more than one bone and more than one part of the body, as typical examples were patients with fractures of both femurs and a radius, femurs and both tibias, dislocation of the shoulder and fractures of the clavicle, 4 ribs and the os calcis of both feet The second characteristic was that most fractures were

compound Of the 1,285 fractures, 1,062 or 83.6 per cent, were compound A third characteristic was the fact that most of the fractures were shatter fractures with marked fragmentation of the bone, but without much displacement Often only one of two bones was broken

The problems of fracture care in battle casualties aboard the Hospital Ship were varied First, and perhaps most important, was the care of the wound, and in compound fractures wound care did not differ from that described for other wounds Secondly, the patient had to be immobilized so that he could be moved painlessly from shore to ship and from ship to shore, and, if necessary, at a moment's notice to lifeboats or liferafts It was apparent then that no form of traction which necessitated weights or pulleys could be used Therefore, all fractures were treated in plaster, often with the addition of skeletal fixation by means of pins or Kirschner wires Plaster immobilization was adopted for the further reason that traction was out of the question because of the movement of the ship and because of the number of cases During one period there were aboard 22 patients with compound fractures of the femur

Internal fixation was used in only 4 cases In two patients screws were applied to fix fractures of the epicondyles and in two cases of fractures of the forearm plates were applied In none of these was the wound sutured The Roger Anderson apparatus was available for use throughout the entire period in which casualties were being received It was used in only two cases

Unpadded casts were used in the care of fracture cases Felt pads were placed to protect bony prominences and vaseline was applied over the skin to prevent the hair from sticking to the plaster No form of padding was used, however In a few cases it was necessary to split the cast after it was applied, and in all cases the circulation was carefully watched, but no complications arose from the use of unpadded plaster casts in our hands In order to preserve the cast in patients whose large wounds produced profuse drainage, it was necessary to make windows over the wounds so that absorbent dressings could be changed as required Although this took away some of the advantages of the closed plaster method, it seemed the lesser of two evils, otherwise the casts had to be changed because of softening in a matter of 2 or 3 days

CHEST WOUNDS

Chest wounds represented 7.4 per cent of the total wound group,

but only about half of these showed intrathoracic injury. It was evident that the chest cage protected the patient against intrathoracic trauma in many of the wounds resulting from low velocity missiles. Through and through wounds of the chest were not uncommon from bullets, and it was surprising to note the relatively little intrapulmonary damage that was produced in these cases. Even the presence of intrathoracic foreign bodies produced few clinical or X-ray findings.

Fractures of the ribs and scapula were quite commonly associated with chest wounds. In patients with hemothorax it was found that the pain and fever were increased by repeated tapplings so that it became our policy to reserve this procedure for those cases in which there was dyspnea or in which infection was suspected. Sucking wounds were not common and in most cases they were treated by packing and in only one case was suture performed.

WOUNDS OF THE ABDOMEN

Wounds of the abdomen represented 2 per cent of the wound group, but it must be remembered that wounds of the loin, back, and perineum also frequently produced intraperitoneal injuries. All of the patients who came to us had been operated upon before they reached our hands. It became apparent from observation of these cases that suture of the wounds of the stomach and small gut gave a much better prognosis than those of the large gut. Many of the patients in whom intraperitoneal injuries resulted from wounds received from the back, had large retroperitoneal hematomas which appeared to do well without drainage. Most of the abdominal wounds which were sutured after operations upon the large gut became infected and broke down, hence it seemed to us that no effort should be made to close the skin and subcutaneous tissues in these cases, and we recommended suturing the muscle and fascia with stainless steel wire and wound packing following the application of sulfathiazole locally.

VASCULAR INJURIES

In the treatment of battle casualties with large wounds, secondary hemorrhage not infrequently occurred. We rapidly learned to be constantly on the lookout for this complication so that immediate treatment could be given. Hemorrhage occurred in 13 cases, in 8 of which it was necessary to take the patient to the operating room for a liga-

tion of the bleeding vessel. Another vascular injury which was observed in 10 cases was pulsating hematoma. This was seen most often in the thigh, but occurred also in the neck, arm, forearm, and lower leg. Because of a severe hemorrhage which occurred in our first group of patients, we afterwards performed ligation and excision of the injured artery and vein in such cases. These operations were performed on the average from 8 to 10 days after injury. In our group of cases there were 5 of the femoral artery, one of the brachial artery, and one of the radial artery. In none of the cases was there any evidence of any peripheral arterial difficulty following ligation.

GAS GANGRENE

Aboard the Hospital Ship, 10 cases of clinical gas gangrene, proved by culture, were seen. Of these, 5 died and 5 lived. Two of the deaths occurred two and one-half and five hours after the patients came aboard the ship and one death arose from gas infection that appeared in the stump of a patient who had an amputation performed before he arrived on the ship. Of the other two deaths, one occurred following a mid-thigh amputation of the lower leg where gas gangrene was already present, and the other 12 days after injury in a patient whose thigh wounds had been sutured the day of his injury. Gas gangrene occurred in the muscles of the thigh and lower abdomen, and in spite of the wide incision and intensive treatment, death occurred on the third day after admission to the ship.

Gas gangrene as seen in the South Pacific occurred exclusively in casualties from land battles. It occurred in 10 per cent of 3,333 casualties, but it was the cause of about half of the mortality in these 3,000 patients. It was characterized by a tension type of pain without the production of much gas in the tissues. In several of our patients, gas was not demonstrable in the X-ray. There was not the characteristic discoloration of the skin, or at least this discoloration was not recognized when associated with ecchymosis and swelling. Temperatures varied between 100° and 102°, and the most characteristic laboratory finding, aside from culture, was a very high leukocytosis, which ranged between 20,000 and 40,000. At operation, the tissues presented marked edema and the typical brick red coloration.

In the treatment of gas gangrene, conservatism again was practiced. In those patients in whom there was an evident disturbance of the

blood supply to the part, a guillotine type amputation was performed, and for this operation refrigeration was the anesthesia of choice. During the two hour period of refrigeration all absorption from the infected area is effectively blocked by the tourniquet, and this time may be well used to give supportive and specific treatment. Where there was an adequate blood supply, wide incision was practiced with the local and systemic use of sulfathiazole, immobilization of the part, and huge doses of gas gangrene antitoxin (100,000 to 200,000 units in 24 hours intramuscularly). In our series, this was the method of treatment used for the five patients with gas gangrene who lived.

X-ray was not used as a method of treatment of gas gangrene because the X-ray machines available were not suitable. Penicillin was not available to us at the time. It may be that the use of this therapeutic agent will improve results in this type of infection.

Since returning to the States, penicillin became available as an agent to combat infection in war wounds. We have had an experience with it in a large variety of cases and have seen its almost miraculous results. It has been used both locally and intramuscularly in the late treatment of infected wounds. It is apparent that neither the sulfonamides nor penicillin are any substitute for good surgery. The same surgical principles still hold. Adequate drainage has to be provided, sequestra have to be removed in the same way as before these drugs were available. On the other hand, by controlling infection with penicillin and the sulfa drugs surgical procedures may often be successfully attempted which would have been impossible without their use.

No discussion of the treatment of war wounds would be complete without some mention of the systemic treatment of the wounded man.

The use of plasma in generous quantities and its availability in the front line aid stations has been the most outstanding advance in the treatment of shock in battle wounded. This, combined with morphine and rest, are therapeutic measures that have proved their value.

In many patients plasma administration must be looked upon as a stop-gap until whole blood can be given to replace that lost due to wounds. Little resistance to infection or healing of wounds can be expected in patients with hemoglobin readings of 40 or 50 per cent. We had a living blood bank in the crew of our ship and transfusions were given in liberal quantities until the hemoglobin was 70 per cent or over.

Bed rest, quiet and good food are three other therapeutic measures that aid in the rapid recovery from war wounds. These can only be had outside the battle zone, hence the value of rapid transportation via air or ship to areas of relative safety.

It is apparent that war wounds are not much different from wounds of civil life except that there are more of them. The surgeon who cares for them should remember the dictum of Paracelsus—"Every surgeon should know that it is not he, but nature who heals. The physician is but the helper, who furnishes nature with weapons. The apothecary is but the smith who forges them. The business of the physician is therefore to give nature what she needs for her battle." What I have told you tonight is an example of one effort to solve the riddle of giving nature what she needs in her battle for war wounded.

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THE REACTIONS OF TISSUES
FOLLOWING INFECTION AND THEIR
PLACE IN AN ENVIRONMENTAL
CONCEPTION OF THE NATURE
OF DISEASE *

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WHEN Doctor Jaffe invited me to take part in this centenary meeting of The New York Pathological Society and to share in the program of The New York Academy's Graduate Fortnight, I was greatly pleased. Merely to have been invited was sufficient reason for this, but there were other considerations. In the first place, here was presented an opportunity to meet a group of pathologists, only a few of whom I could call personal acquaintances, in the second place, the occasion offered an enviable opportunity to discuss one of my major interests with a group of critical colleagues, in the third place, your Graduate Fortnight is one of the few occasions on which pathologists are recognized for what they really are, students of disease, and are brought together with their clinical colleagues to acquire through the medium of critical reviews a more intimate knowledge of current problems in the science of medicine.

I do not flatter myself by thinking that I can announce to a company of this sort a new set of general pathological principles which underlie the reactions of tissues to infectious agents. Through great familiarity with disease processes, you all know too well those few essential biological responses to stimulation which characterize mammalian tissues to expect such a thing of me. Nevertheless, through a reexamination of certain ones of our well known pathological principles, and thus, through the exposition of a certain point of view, somewhat novel though that point of view may seem to you, perhaps I can pay you at least in part for the nice compliment which you have paid me through your invitation to this meeting.

* Read before the Centenary Meeting of the New York Pathological Society in connection with the Seventeenth Graduate Fortnight of The New York Academy of Medicine, October 19, 1944

During the past fortnight, you have heard interesting and instructive accounts of the progress which is being made in the study of certain practical aspects of infectious disease. You have had reviewed for you those really amazing procedures that have been developed for the control and, indeed, the cure of such plagues as gonorrhea, pneumonia, syphilis, and certain meningococcal and streptococcal infections, perhaps, even the arch enemy of the young, acute rheumatic fever, may be included in this list. These accomplishments have come through the hard thinking and drudging labor of colleagues who no longer put their trust in empiricism and favorable accident, but who, instead, build according to plans and specifications dictated by established basic biological principles. In the discussion you have heard, the emphasis, by plan, has been placed on the practical and, indeed, timely problem of the *specific treatment of specific disease entities* produced, as we are accustomed to say, by *specific etiological agents*. Under a bombardment of this sort, particularly in the face of the urgencies of the times, it is natural to think of disease almost solely in terms of the *specific living things* which we say *cause* disease and in terms of the *specific dose of poison*, so to speak, which we may administer to those living things to dispatch them. Biblically speaking, our chief objective for the moment has come to be the casting out of the parasitic devils! In normal times, when there is no insistent O S R D and thinking and working is more deliberate, there is less tendency to forget that, though the earth and the firmaments may be asquirm with the seen and the unseen living agents of disease, *where there is no host for these potential parasites there can be no disease*. And so, there is some purpose, and perhaps momentary relief, in having discussed for you at the conclusion of this fortnight that most important factor in infectious disease, the host.

The one who would attempt to understand disease has his attitude towards its problems determined well in advance by his conception of the basic nature of disease. Since what I propose to say regarding tissue reactions in infectious disease is in the nature of an attempt to understand disease, it is necessary for me to lay before you my own conception of the nature of disease before going forward with the development of the main theme which has been selected for this presentation.

I have been able to find no broader attitude toward the problems of general biology, a branch of which medicine surely is, than that expressed by Claude Bernard, he has put the matter this way

"As the essence of things must always remain unknown, we can learn only relations, and phenomena are merely the result of relations"

Being confident that this great man's mind penetrated to the core of things biological, I have been quite willing to accept his view that we can learn only relations and so have formulated my own conception of disease as follows *Disease is a matter of the abnormal outcome of a constantly changing relation between the ultimate biological unit, the cell, and its environment*

This environmental conception of disease is comprehensive enough to permit emphasis wherever it may be appropriate. It is sufficiently restrictive to enforce proper consideration of all the factors which enter into the relationship. It permits of no dissociation of injury and reaction to injury, and it makes of etiology and pathogenesis an entity which cannot be disrupted without destruction of the whole concept.

Lest some of you become a bit impatient with this seemingly impractical consideration of the matter, let me show you how this concept of disease may be applied to that large group of important infectious diseases characterized by the invasion of the body by the viruses. Nobody questions the existence and the etiological significance of certain substances now identified with some of the more typical diseases that belong to this group and called viruses, and yet, with one or two exceptions, we know virtually nothing about most of these substances except what we have learned by studying the *relation* between them and the host cell. We identify them in almost every instance by studying *not the virus* but *the reactions of the host cells to the virus*, that is, the host-parasite relationship. Improvements in techniques may make it possible in the future to study the physico-chemical constitution of all of the viruses isolated in highly purified states, as already has been accomplished with a few of them, but this would not guarantee us a better understanding of the diseases to which they are related. A crystalline virus in a test tube is indeed an important little cosmic unit, but that intratestubal relationship is very different from the obligate cell-parasite relationship which comes into being when a virus characteristically takes up its residence within a living cell. In the diseases produced by these agents, the physical and biological relationship that exists between the virus and the host cell is so intimate and so mutually essential that, in one's thinking, there is no possibility of divorcing the agent from the

cell, therefore, the study of both the virus and the disease caused by the virus turns out to be nothing other than the study of the outcome of a very intimate and complex intracellular host-parasite environmental relationship. Under these circumstances, it is only natural in considering the nature of the viral diseases to place the emphasis upon the reaction of the host cell rather than upon the virus which provokes that reaction.

Having been impressed by the greater importance of the cell reactions in the viral diseases, I have thought that it would be profitable to look into the matter of the host-parasite relationship which obtains in the common bacterial diseases to determine whether or not a comparable situation exists in these infections. Wherever I have turned for materials for study of the problem the outcome has been the same. My own continuous study of ever recurring human and animal infections, the studies of experimental infections carried out in my own laboratories and in the laboratories of many colleagues, the critical reviews of others who have interested themselves in the problem and the investigations of workers in the basic biological sciences, all, have been found to point in the same direction. In the final analysis, it seems that the greatest advantage is gained by using the reaction potentialities of the cell as the keystone in the building of a satisfactory conception of disease.

Some of our clinical colleagues, I am sure, will not accept this emphasis without vigorous protest, and their protest has a right to be heard. They, like we, know that we cannot breed disease-resisting strains of human beings as the intelligent farmer breeds his cattle and his corn. They know that they must accept man as they find him. They know from many trials and errors that what little they may undertake to do in the way of changing the basic reaction potentialities of the tissues often turns out badly. It, therefore, appears to them to be more practical to give first consideration to the extrinsic etiologic factors in disease causation. It is not difficult to join in these protests because experience has shown that at least in a few instances it is possible to prevent disease simply by eliminating the parasite from the environment of the potential host. In some instances it is even possible to destroy the parasite within its host. Along with our clinical colleagues, we might be content to enjoy that chronic optimism which their successes with the prevention and treatment of a few of the more spectacular infectious diseases pro-

vides if it were not for that large group of diseases that bedevil us during the last half of our three score years and ten. Our almost complete helplessness in the face of these diseases is sobering, to say the least, we need no more potent stimulant than that offered by this helplessness for a more thoughtful consideration of those internal factors in disease causation which, for the moment, we may call the reaction potential of the cell.

As we shall see presently, no parasitic infection is a simple killing matter such as is the blow of the guillotine knife. Whatever the parasite may be, the disease produced by it is a time-consuming process. That which takes place as time runs on—hours, days, months, or years as the case may be—as I see it, is determined almost solely by the cellular reactivity of the host. As far as I can find out, there are no fundamental changes that take place in the parasite during parasitic disease, the invader remains essentially as it was the day it entered the tissues *except in so far as it may be altered by the reactions of the host tissues*.

If tissue reactivity in disease is as important as I have attempted to make it out to be, a definitive description of this reactivity should be presented before proceeding further, otherwise, the whole discussion might degenerate into a mere metaphysical exercise. This I shall try to do for you briefly.

Admittedly with some danger of over simplification, I have found it useful to view the reaction potential of cells and tissues as follows. When cells or tissues are injured they may react in four essential ways.

- 1 They may submit more or less passively to the injury and thus go through the process of dying and disintegrating.

- 2 They may react in such a way that they protect themselves and other tissues against further injury, thus playing a sort of automatic defensive role.

- 3 Under certain conditions of injury they may become so adapted through alterations in their functions and structure that they effect a compensatory adjustment for losses of function by other related tissues and thus make it possible for the individual of which they are a part to remain in comparative equilibrium with its environment.

- 4 They may undergo a basic alteration in their reactivity which makes them more highly susceptible to injury by a given agent than they originally were.

At once it will be apparent to you that the submissive and the de-

fensive reactions of tissues are most apt to occur immediately following injury, they usually take place in the presence of the specific agent producing the injury. The reaction of adaptation may be immediate and direct, but, in its most impressive form, it is a secondary phenomenon which takes place after a primary injury in an entirely different but related tissue has occurred. The hypertrophy of the heart muscle which results from the increased work requirement created by an injured and incompetent valve is a good example of this. The reaction of sensitization takes place only under rather specialized conditions of injury, and it is dependent upon actual contact of the cell with the injurious agent, its complete development is always delayed.

Here a word of caution is necessary. In any given pathological situation one may find all four of these basic reaction types represented. As a rule, however, one of them dominates the situation and thus gives a certain character to the disease entity in connection with which it occurs. Because of this, it is possible and, as I see it, quite useful to classify our common disease entities on the basis of the prominence of one or another of the basic reaction types which characterize these entities.

In order that this discussion may be brought into more proper reference to the occasion I shall now do three things. First, I shall focus your attention upon the environmental relationship which exists between the cell and the surrounding fluids in an area of injury by bacteria, this will serve the double purpose of emphasizing the importance of the environmental conception of disease processes and of bringing into relief a few of the more interesting types of cellular reaction. Second, I shall make a few pertinent comments on the somewhat peculiar reactions of certain tissues which are becoming more and more prominent as the most probable basis of some of our least-well-understood diseases. Finally I shall make a few comments on the nature and classification of infectious diseases especially as determined by the basic reactivity of the tissues.

In infectious disease, opportunity is presented for the study of reactions which involve all kinds of cells, those most conspicuously implicated are determined by the extent of the invasion of the infectious agent. At the site of entry of infectious agents and at all points of subsequent localization, an environmental situation develops which gives rise to all the basic forms of cellular reaction. The total effect of these

reactions may be considered to be resistive and hence, with reference to the individual, defensive. We call this situation inflammation. It will serve our purposes to examine this environmental situation with some care. In so doing, however, we need not undertake a consideration of all the important aspects of this vital response of the tissue to injury.

The presence of an infectious agent in the tissues changes the local environmental relationships in one or more of three essential ways. First, it alters the fluid medium in which the cell must live, second, it may give rise to a specific alteration in the basic reactivity of the cell, third, it may change the cytoplasmic and nuclear structural and functional constitution of the cell. A few illustrations will help to clarify what I mean.

First, let us examine the environmental situation which develops when a type III pneumococcus is introduced into the tissues of a rabbit. This animal, as you may recall, usually is not seriously harmed by this organism, although a sharp local reaction is provoked. In the animal which possesses only its natural resistance to injury by this organism, the pneumococcus finds in the fluid environment of the host cells all its metabolic requirements, and, within the first few hours, it is relatively undisturbed in its propagation and spread. The relatively unrestrained growth of the organism quickly alters the character of the intercellular fluids in a profound way. Not only do the living organisms discharge their products of metabolism into these fluids, but also those organisms which do not survive disintegrate and contribute their own basic chemical substance to the environment. Since the basic metabolic requirements of bacteria and cells are the same, the living organisms create a local cellular nutritional imbalance by competing with the living cells for the nutriments available in the common environment. Important changes occur also in such factors of the fluid medium as the ionic concentration, osmotic pressure, hydrogen ion concentration, viscosity, *et cetera*, and, what is additionally significant, these changes may involve all the circulating fluids of the host. This change in environment is incompatible with the normal functions, even the life, of both the fixed tissue cells and the freely wandering cells of the fluid and tissues. This being particularly true of the capillary endothelium, the environment becomes further altered by the excessive transference of fluids to the tissue spaces and, indeed, by the extravasation of whole blood. Up to this point the pneumococcus has had its own way with the exception

of a restriction of its spread from the area of primary injury through the action of certain mechanisms of natural resistance the details of which need not concern us at this point. But, this local change in environmental relationships has its general effects. The rabbit develops a temperature elevation, and, if the experimental evidence does not mislead us,¹ therein lies the undoing of the pneumococcus. The new local environmental situation created by the temperature elevation makes it impossible for the pneumococcus to continue to produce its capsules. These unprotected organisms then become the victims of leukocytes whose normal phagocytic activities previously had been thwarted by the barrier which the capsular substance offers to phagocytosis. Thus, it appears that a change in a single factor of the environment of the cell results in a complete reversal of the cell-bacterium relationship, and the infection quickly comes to an end.

Infection of a rabbit with a virulent type I pneumococcus provides an excellent opportunity to study another type of alteration in the environmental relationship of cells, one which involves an entirely different set of factors from that just discussed. If this organism be introduced into the skin of a non-immune rabbit, the animal develops a bacteriemia within a few hours and dies. If the tissues at the site of inoculation are studied histologically, it will be found¹ that the organisms spread rapidly and diffusely through the tissues as they proliferate and that they produce grave injury to the tissues. Phagocytosis of the organisms is minimal. In animals previously exposed to pneumococcus I infection or passively immunized, the situation is very different. Histologic study of the tissues of these animals reveals a localization of the bacteria and a tendency of the organisms to grow in clumps. Furthermore, there is active phagocytosis of the organisms by the reacting leukocytes. It is obvious that the immunized animals are effectively protected because they survive the infection. We know that this is accomplished by adding something to the cellular environment which not only facilitates phagocytosis but also brings about clumping and restraint of spread of the growing organisms. [There appears to be no interference with the growth and propagation of the bacteria except that referable to phagocytosis and digestion by the leukocytes. This is indicated by the fact that immunized animals deprived of their leukocytes die of the infection just as do the non-immune animals¹] This alteration in the fluid environment of the cells appears to be the result of a specialized

form of cellular activity, that is, specific antibody production [We do not know just what cells are concerned in this alteration of the environmental fluids, but we are assured that those at the site of infection are not solely responsible ²]

In the preceding paragraphs, emphasis has been placed upon some of those changes which take place in the fluid surrounding the cell that are responsible for an alteration in the cell-bacterium equilibrium. It was pointed out that some of the changes are referable to the bacterium and some to the reacting cells. Next, I shall discuss the second way in which entry of bacteria into the tissues gives rise to significant disturbance in the environmental relationships of the tissues, this consists of the stimulation of a specific alteration of the basic reactivity of the cell, and it may or may not result in the *addition* of something to the environmental fluid. As you may surmise, I refer to the development of what we call tissue sensitization.

It is necessary at this point to recall that there are two types of tissue sensitization that arise in the course of bacterial infection. These differ in what appear to be fundamental ways. I refer to a) anaphylactic sensitization, with which may be included that type of cellular alteration which underlies the Arthus phenomenon, and b) bacterial allergic sensitization, the best known example of which is that out of which arises the tuberculin reaction. Zinsser³ was the first to emphasize the differences between these types of sensitization. Rich, in his recent monograph on the pathogenesis of tuberculosis,⁴ has outlined the matter in his Table XVIII which I have taken the liberty to reproduce (Table I). For our immediate purposes we need refer to only one of the differentiating features cited in this table, that which relates to the blood serum or, more specifically speaking, to the medium surrounding the cells. In the case of anaphylactic and Arthus sensitization, the fluid environment of the cells is altered by the *addition of antibody* just as it is in the case of immunization of the rabbit to the pneumococcus cited above. As a result, the environmental relationship thus set up by the infection may be transferred from an infected animal to an uninfected one, and when the cells of the latter are subjected to contact with the specific antigen they react quite like the cells of the former. This situation does not prevail in the case of bacterial allergic sensitization. The alteration in the environmental relationship which occurs in this form of sensitization is referable to a change in the basic reaction potentiality of the host cell.

TABLE I

THE CHARACTERISTICS OF THE TYPES OF HYPERSENSITIVITY
 Illustrating the similarities of the anaphylactic, Arthus and pollen types, and their differences from the tuberculin type

			Type of Hypersensitivity			
			Arthus	Anaphylactic	Pollen	Tuberculin
Usual <i>minimum</i> requirement for establishment of sensitivity	Single parenteral contact with small amount of free antigen		0	+	+	0*
	Parenteral contact with repeated small amounts, or with a single large amount, of free antigen		+	0	0	0
	Parenteral contact with intact bacteria or virus		0,	0	0	+
Some of the clinical effects that may result from contact of the previously sensitized body with the specific antigen	Prompt local oedema, erythema, foll by haemorrhage, inflammation, necrosis		+	0	0	0
	Prompt, evanescent, local oedema and erythema		++	+	+	0
	Generalized oedema		+	+	+	0
	Generalized urticaria		+	+	+	0
	Symptoms of asthma (dysp) or hay fever (nas fulness, lacrymation)		+	+	+	0
	Prompt, fatal anaphylactic shock		+	+	+	0
	Prompt, non-fatal constitutional reaction		+	+	+	0
	Delayed constitutional reaction, fatal or non-fatal		0	0	0	+
	Delayed and prolonged local inflammation, and necrosis		0	0	0	+
Evidence for site of action of antigen in sensitized body	Action directly on extra-vascular tissue cells	Necrosis of cells on contact with antigen <i>in vitro</i> (tissue culture)	0	0	0	+
		Necrosis of cells in avascular tissue <i>in vivo</i> (cornea)	0	0	0†	+
	Action on capillaries	Increased capillary permeability (local oedema)	+	+	+	+
		Necrosis of capillaries with haemorrhage	+	0	0	+
	Action on involuntary muscle	Spasmodic contraction of involuntary muscle <i>in vivo</i> and <i>in vitro</i> (Dale bath)	+	+	++†	0
Body sensitized to a bacterial protein reacts hypersensitively to the intact bacteria			0	0	—	+
Passive transfer of sensitivity readily accomplished			+	+	+	0

* See text for possible exceptions

† Not tested

‡ With small dose of antigen

which involves factors that are inseparable from the cell body. It is especially interesting to note that in certain types of bacterial allergic sensitization (tuberculin sensitization) the sensitized cells will grow and reproduce themselves in normal serum (*in vitro*) and transmit their sensitivity to their daughter cells.⁵ This would seem to indicate a genuine constitutional alteration of the cell in the course of allergic sensitization. We are reminded, in this connection, of the constitutional factors that appear to be almost regularly involved in the sensitization of bronchial asthma, and of certain food allergies. It is the stimulation of these anaphylactic and bacterial allergic reactivities of the cell that I wish to call attention to as the second previously cited mechanism through which the invasion of the body by bacteria changes the environmental relationship within the tissues. Reference to the accompanying table will show how important the environmental situation created by hypersensitivity is, especially as it may influence the reactivity of the endothelium and smooth muscle, that is the vascular system.

I have cited for you some of the essential changes that may take place in the environmental relationships of the cell following the entry of bacteria into the tissues particularly as they relate to the composition of the environmental fluids and to the basic reactivity of the cell and have suggested to you some of the significant effects of these environmental changes. For the sake of completeness, a few words should be said relative to the changes that may occur in the environmental relationships through alterations in the structural and functional constitution of the cell which are not immunological. My point in this connection can be made most effectively by reference to the viral and the rickettsial infections.

In the viral and rickettsial diseases we deal with an extraordinary form of parasitism which has as its chief characteristic the intracellular residence of the parasite. Properly to understand these infections it is necessary for one to carry the environmental concept quite beyond the level of the cell and to think in terms of the relation between the physico-chemical constitution of the nucleus and the cytoplasm of the cell as it may be related to the physico-chemical structure of the particular agent concerned. I have no intention of entering into a discussion of this problem for the very simple reason that I know very little about it. Nevertheless, by way of illustrating my point, I can cite for you the most important alterations in cellular reactivity that arise out of the

disturbance in the intracellular environmental situation that is created by the invasion of the cell by, for example, a virus. Briefly they are (1) increase in reproductive activity resulting in an extraordinary hyperplasia, (2) alteration of the metabolism of the cell in the course of which specific antibody is produced, (3) profound alteration in the basic growth potentiality of the cell resulting in a condition indistinguishable from genuine anaplasia, (4) death and disintegration of the cell.

For our clinical colleagues there is an important practical consideration involved in this matter of intracellular cell-parasite relationship. We are all familiar with the ineffectiveness of the treatment of the viral and rickettsial diseases by our new chemotherapeutic substances, the sulfa drugs and penicillin. It is not improbable that the very striking difference between the effects of these agents upon the bacterial and the viral and rickettsial diseases is due in part to the fact that in the latter the therapeutic agent may never reach the parasite for which it is intended, or, perhaps, it reaches a parasite which is doubly protected from the drug, first by the surface constitution of the parasite itself and, second, by the barrier of cytoplasmic or nuclear protein which surrounds the parasite.

Passing now from a consideration of the environmental relationships of cells as they may be altered by the entry of infectious agents into the tissues and the potential changes in basic cellular reactivity that result from these environmental alterations, I shall next say a word or two about the somewhat peculiar reactions of certain tissues which appear to be particularly susceptible to alterations in their reactivity when the environmental relationships become disturbed by infection. These tissues are the blood vessels and the connective tissue. I select these tissues for two reasons. In the first place, they are concerned importantly in practically all forms of inflammation *immediately* resulting from invasion by infectious agents and, in the second place, changes in the reactivity of these tissues play an essential role in certain delayed manifestations of infection the full significance of which is only just now coming to be widely appreciated.

I can make my point with regard to the reactions in the blood vessels that are directly and immediately incident to the invasion of the tissues by infectious agents by very brief statements. The vascular aspects of the inflammatory reaction are too familiar to every one to require more consideration. The essential vascular reactions relate to

the endothelium and to the nerve-muscle structure. The results of these reactions are an increase in permeability of the endothelium to all the components of the blood—including, it may be emphasized, circulating antibody—accompanied, if not actually preceded, by a marked dilatation of the vessels. Injury of the endothelium is followed by thrombosis and circulatory obstruction, and death of vascular muscle and connective tissue results in hemorrhage. These reactions, which are essentially submissive, are followed by a marked proliferation of endothelium, connective tissue and even muscle (the formation of granulation tissue), essentially a compensatory process. All of these reactions and their importance are so familiar to you that nothing more need be said about them.

Connective tissue we recognize to be the common clay, the filler, or the matrix of body structure, but, even so, it is composed of potentially the most highly reactive cells that go into the structure of the body. Because of this, connective tissue almost always is involved wherever tissues react to injury. Only the immediately killing injuries can take place without provoking a literally speaking “reactive” response on the part of connective tissue cells. The two most common reactions of connective tissue cells are the two extremes, proliferation and death and disintegration. A consideration of both of these reactions can be used profitably in the further development of our theme.

In all destructive injuries to tissue, the local cellular relationships become quite complex, in this, fibroblasts are conspicuously involved. Let us consider for a moment the situation which arises in the course of the formation of a simple bacterial abscess. At the margin of this lesion, a proliferation of fibroblasts occurs and continues, so to speak, so long as there is *need* of these cells for the reestablishment of the continuity of the tissues. I realize that the conception of *need* as a stimulant for the proliferation of tissue cells is an annoying abstraction, but I know no other way of putting the matter since nobody really knows why these cells proliferate. The only at all satisfactory reason for the growth of the connective tissue cells is a very general one, namely, that there exists locally an environmental situation involving a variety of factors which makes a change in the spatial, structural and functional relationships of the surviving cells necessary if tissue equilibrium is to be reestablished—that is, if the lesion is to heal. [All of this adjustment takes place quite automatically, therefore, just because the word *need*

has been used in this connection, it is not necessary to become disturbed by the conventional fears of a teleological influence creeping into our conception of tissue reaction]

My chief reasons for selecting this particular reaction of the connective tissue for discussion is that it provides an opportunity for me to comment upon the environmental relationship represented by the encapsulation of an infected focus by fibrous tissue proliferation. It is generally said that the body protects itself against infection by the encapsulation or "walling off" of the infected area by newly produced fibrous tissue, a fibrous capsule about an abscess, thus, is said to constitute an effective barrier to the further development and spread of the infection. As I see it, the capsule of fibrous tissue is there not because of a *need for protection of the tissue*, but because the other genuinely defensive mechanisms (phagocytosis, natural immunity, et cetera) have operated so effectively that the invaders are restrained and eventually destroyed, thus creating a new local environmental situation which in its turn constitutes a *need* of an entirely different sort from that just mentioned, *a need for the restitution of the local tissue equilibrium*. This is met through the proliferation of fibroblasts at a far greater rate than is the rate of destruction of these cells, the result is the encapsulating fibrous membrane. The formation of the capsule of an abscess, thus, is merely the expression of healing of the lesion and, therefore, is nothing more or less than the formation of a scar. As far as I know, there is no indication that scar tissue is particularly resistant to destruction by bacterial action.

In the preceding comments on fibrous tissue reactions accompanying infection, the emphasis has been placed upon local tissue relationships which result either in fibroblastic proliferation and fibrosis or in death of connective tissue cells. A far more interesting relationship involving connective tissue reactions following infection and related processes is that out of which arises a slow and even sublethal degenerative (sometimes quite dramatically and acutely necrotizing) reaction of the connective tissue, particularly the reaction of the collagen fibers. I refer to that peculiar change in the mature connective tissue, chiefly that in the blood vessels, in the endocardium and in the membranes lining and adjacent to the joint cavities which we know as *fibrinoid or hyaline degeneration*. We know ever so little about the environmental situation which gives rise to this reaction, but its effects are quite familiar to us

The whole matter is a live issue just now and has been for the past two decades. The more we learn about it the more apparent it becomes that we must go back to the early studies on the phenomenon of tissue sensitization to get our leads to its understanding. To follow the thread of argument in support of this view of the matter is not possible at this time, so I shall ask that you be content for the moment with the suggestion of the basic idea and permit me to proceed to the concluding part of this discussion.

What remains for me to say chiefly consists of a comment on a group of disease entities underlying which, we now have good reasons to believe, is an environmental situation characterized by varying degrees of tissue sensitization to proteins, some of which surely are *bacterial* in origin.

I have devoted the bulk of what I can say regarding the reactions of tissues following infection to those reactions which can be dealt with best at the level of the cell. Since, after all, there are very important practical considerations involved in the study of disease that relate to the summation and integration of all the cellular reactions, that is to the individual reacting as a whole, it will be useful to say a few words about types of infectious disease as they are determined by the reactivity of the tissues arising out of infection.

Basing our ideas upon the reaction potential of the tissues in the face of infectious agents, it is possible to see the infectious diseases as falling naturally into two groups as follows.

Group I Diseases in which the conspicuous tissue reaction is *direct and immediate* following the invasion of the infectious agent through what we all know as acute or chronic suppurative and chronic granulomatous inflammation. Good examples of these are pneumonia, peritonitis, purulent meningitis, and primary tuberculosis.

Group II Diseases in which the reactions of the tissues to the infectious agents are *indirect and often if not characteristically delayed*. These diseases are chiefly the result of the submissive (alterative or degenerative) type of reaction of the tissues to injury. The typical injurious agent is an initially non-toxic chemical substance derived from the infectious agent which becomes highly toxic as a result of the development of tissue sensitization. To this group of diseases, we have good reasons to believe, belong certain types of bronchial asthma, acute rheumatic fever, periarteritis nodosa, acute and chronic diffuse glomeru-

lonephritis, certain types of chronic arthritis, and (perhaps) lupus erythematosum disseminatum. Certain forms of tuberculosis, perhaps chronic brucellosis, some of the mycoses, and some of the other genuinely granulomatous diseases, with some justification, might be included in this group.

I shall not bother you with any further reference to the disease entities which fall into Group I since the problems of pathogenesis they present are not novel, though many of them are far from adequate solution. Nor do I think it profitable to review the essential problems in the pathogenesis of those diseases of Group II which are more or less accepted as examples of bacterial sensitization. Instead, I wish to leave with you the suggestion that in the principles involved in the pathogenesis of those diseases now accepted as arising out of the cellular environmental situation created by bacterial allergic and anaphylactic sensitization we *may* have the key to the understanding of some of those disease entities which still defy pathogenic analysis. Outstanding among these is a group of so-called *degenerative* diseases. The feature common to all of these is a necrotizing disintegration, sometimes very slow and sometimes even explosive, of the connective tissue and its embryologically closely related substance, smooth muscle. This, in some of its several histologic forms, resembles strikingly the fibrinoid or hyaline degeneration that is so characteristic of those diseases which we have good reason to believe are related to bacterial or other types of sensitization. The diseases referred to are (1) eclampsia, (2) bilateral massive cortical necrosis of the kidneys, (3) medionecrosis aortae idiopathica, and (4) the sphinx of all the so-called degenerative diseases, arteriosclerosis.

In what I have had to say to you, my chief objective has been to lay before you a point of view. Since a point of view is after all an abstraction, and abstractions are never easy things to deal with, with the hope of giving the point of view in question some semblance of concreteness, I should like to reduce the matter to a schematic representation for you. The environmental relationship out of which disease arises is represented in the accompanying drawing.⁶ The diagram represents a complex individual separated from the great unlimited *external environment* by a living zone of exchange. In the center is the ultimate biological unit, a living cell, which is surrounded by a complex but limited *internal environment*. The prevailing condition is the state of health characterized by an equilibrium between the factors of the internal

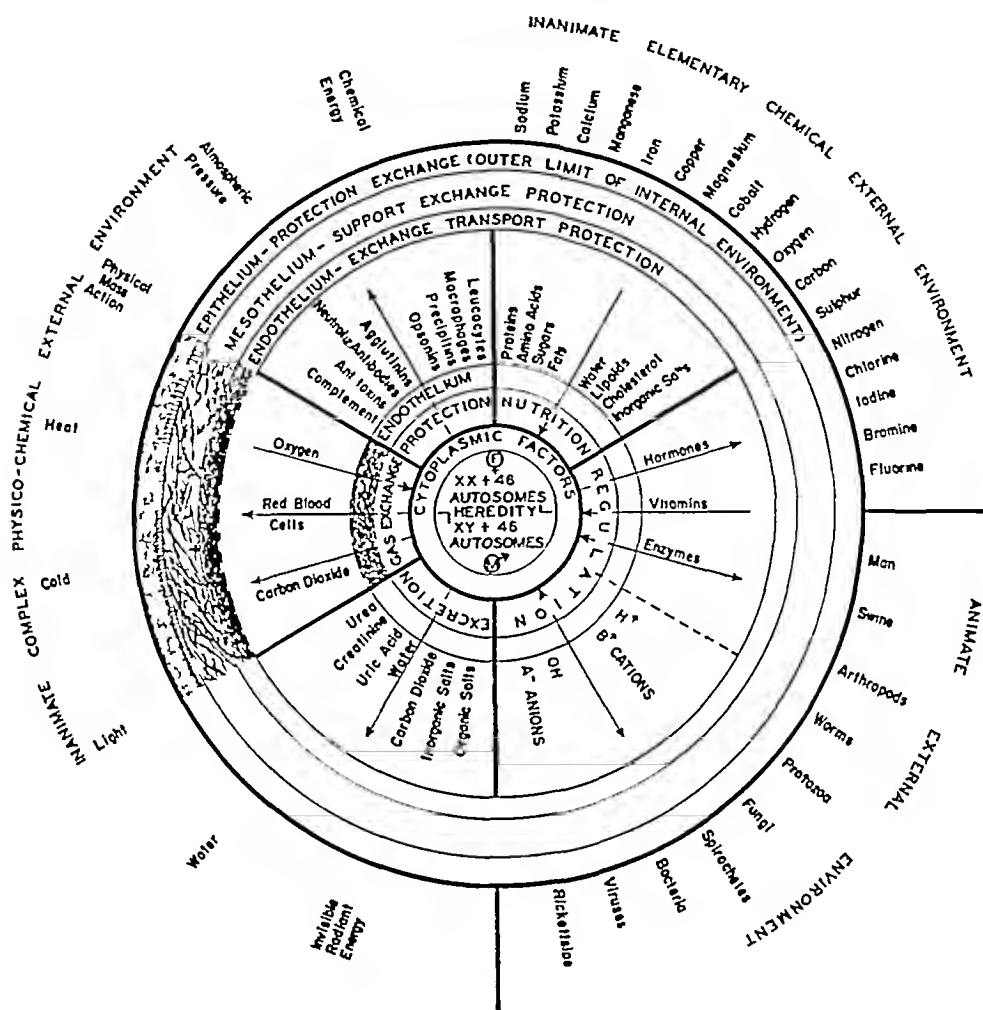


Fig 1—Reactions of tissues following infections, etc.

environment and the factors of the external environment

Beginning at the periphery and passing to the center of the drawing, the concentrically arranged zones and what they represent are as follows (1) The external environment, the unlimited outer universe—In this zone exists the animate and inanimate factors concerned in health and disease. The relative importance of the external environmental factors in the health equilibrium is presented roughly by the length of the corresponding segments of the circumference. (2) The outer zone of the exchange between the individual and the external environment—In this zone are included the two outer, limited, concentric areas in which reside certain important factors that influence the rela-

tion between the individual and the outer world, namely, protection, support and exchange. These factors are represented anatomically by the epithelial and mesothelial tissues. (3) The inner zone of exchange between the individual and the external environment—This zone is the area between the two concentric, shaded circles designated “endothelium.” In this area are the continuously circulating fluids which surround the cell. Physically and chemically speaking, this is the internal environment of the cell, which represents the simplified individual. The factors which reside in this zone are many, but they all fall into five major groups, excretion, regulation, etc., as indicated. The physical and chemical components of this internal zone of exchange originate either in the individual, that is, in the cell, or in the external environment, as indicated by the arrow points. (4) The innermost zone represents the simplified individual, the cell—This zone is bounded by the black circle which represents the cell membrane, within this is the innermost circle, which represents the cell nucleus. In this innermost zone resides the ultimate factor which determines the balance between the individual and the outer environment, this factor is the individual constitution, which is determined by the chromosomal and cytoplasmic make-up of the cell, that is, by heredity.

In concluding, I should like to state again the point of view the presentation of which has been the main objective of my discussion. Disease is not a simple killing affair. It is a matter of the abnormal outcome of a constantly changing, infinitely complex relation between the ultimate biological unit, the cell, and its environment, and, by corollary, the etiology of disease, more specifically speaking, infectious disease, is not *an organism*, but is *a relationship between an organism and a cell*.

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* The author will furnish a complete bibliography upon request.

LIBRARY NOTES

MEDICAL LIBRARIES AND MEDICAL HISTORY*

GERTRUDE L. ANAN

Medical libraries play an important role in the history of medicine, for the library has always been the parent of historical study. Through the library the records of the past have been preserved and historical research made possible. Through the library such study has been fostered and stimulated. In earlier days only those who made scholarship their career had the leisure and the necessary background, while in the cloistered halls with manuscripts chained to desks, welcome was accorded to a privileged few. The introduction of printing, the publication of texts in the vernacular, the vast increase in the number and size of libraries, has made historical study available to everyone.

Time, however, is even now an obstacle to all but the professional historian, and it is as much a problem to most medical librarians as it is to the busy physician. Few can spare more than a fraction of their time away from the pressure of current or routine duties. Yet for the library to play its proper part, time of both medical man and librarian must be consumed. Only through such cooperation can their aims be realized.

In the building of a collection of books, it is with the advice of those who are to use them that the librarian can achieve the best results. Every library, large and small indicates in its holdings a line of development, but this must be coordinated with the needs of its readers. Every want can of course not be satisfied, but each suggestion is welcomed and considered. The physician interested in the history of his

specialty can better determine the value of a contribution to it, while the librarian in reading secondhand book catalogues can bring to his attention desirable items offered for sale which might be wanted for his personal library. Through such joint assistance competition may be avoided and the librarian will not duplicate volumes expected at a future date to be presented to the library.

The physician, too, can help the librarian. In a plea for the preservation of the memorabilia often carelessly hidden away in homes of the families or descendants of physicians. These, the records of today, will be as valuable to the historians of this era as the documents of past centuries are to those of earlier periods. Too often correspondence, minutes of medical organizations, documents, diaries, announcements and advertisements of seemingly ephemeral interest, have been discarded or relegated to musty attics. The historian realizes that the most unimportant item may have utmost value to the writer of tomorrow, and it should be the responsibility of both librarian and physician to publicize the necessity of preserving such records and depositing them in the library. The paper salvage drive has unfortunately swallowed up much that should have long since been rescued, but there must be more remaining to reward the efforts of the persistent. Important, too, is the attitude of the librarian toward proffered gifts. The Academy Library recently received extremely interesting autograph letters of important medical men of the early nineteenth century.

* Read before a joint meeting of the New York Society for Medical History and The Section of Historical and Cultural Medicine, on November 8th, 1944.

because a university librarian to whom they had first been offered was not properly appreciative. The only possible excuse for not welcoming donations of that kind is the constant problem of every library, lack of space. But surely no additional space will be granted until the urgency of the need is overwhelmingly obvious. There are gifts, of course, that would be out of place in a collection, but a suggestion of a more appropriate depository would convince the donor that the rejection was not based upon a lack of interest, and more fitting offers might be forthcoming.

No medical man of the past is so obscure, no book, pamphlet, or document so worthless that they merit oblivion. Too many of our predecessors were not of this opinion, much to the loss of the libraries. One who saw into the future more wisely than most of his contemporaries was the patron of the Academy Library, Dr Samuel Smith Purple. On our shelves are hundreds of bound volumes of pamphlets which he saved from destruction. These include many American medical theses, a large number published before 1800, contributions by Samuel Bard which are of some rarity to-day, articles by Samuel Latham, Mitchell, Benjamin Rush, David Ramsay, Charles Caldwell and others, besides eighteenth and early nineteenth century tracts by English writers.

I would like to quote from an address delivered by Dr Purple before the Academy in 1877.¹ His words may be familiar to some of you, but surely they bear repeating.

"A popular error exists in the profession, and it has done much to retard the establishment of a good reference medical library in this city. There are not a few who believe that only the best books and latest editions are worth preserving. This idea has tended greatly to retard the growth of our own Library during even the past two years. No book or pamphlet is worthless, every waif from the mental laboratory of the practical physician contains a fact, or, it may be a statement of facts, which, however darkly concealed or obscured by peculiarities of language or description, will

ultimately be unearthed, and serve the genius of practical medicine or medical history. In illustration of the truth of this statement, witness the recent disclosure which your speaker made, first in the Section on Obstetrics and the Diseases of Women and Children, and afterward in this Academy, that more than a century since, Drs Colden and Bard described here epidemics of diphtheria—the scourge of our city in these days.

"The description of this disease by Dr Cobden, in 1753, lies concealed in a somewhat scarce and neglected publication of a long since extinct medical society of London, whilst the description of the epidemic of this disease in this city, in 1770, by Dr Samuel Bard, is contained in this little brochure which your speaker rescued from the press-box of a second-hand paper-dealer in this city *in transitu* to the maw of a paper-mill. Its former owner had sold it for the eighth part of a cent, or at the rate of two cents per pound.

"Will any Fellow of this Academy, from this time forward, despise the day of small things, or consign to collectors of rags or paper stock the pamphlets, or old editions of medical works, which he may weed from his library or garret? Will not all bear in constant remembrance that here, in this our own Medical Home, will be gratefully received and carefully treasured every tract, pamphlet, book, manuscript, engraving, portrait, small or great, which may be donated?"

The Academy Library cannot show gratitude enough to Dr Purple. His efforts in salvaging medical material are not his only contribution. His library, which included 5,000 volumes of American medical journals, was bequeathed to the Academy and served as the nucleus of the collection. His notations, sometimes in separate manuscripts, are of great use to us today. One volume is consulted frequently by those interested either in the first years of the Academy or in the New York medical men of that period. On each page is the name of a founder of the Academy. In Dr Purple's

¹ Purple, S. S. *Medical libraries*
1877, pp 18 19, 25 26

ple's hand are brief biographical notes, references to obituaries or other biographical sketches, and occasionally newspaper clippings containing obituaries. Some give scanty information, but may cite the only record we possess of the men in question. Other of his manuscripts include biographies of well known physicians, a short bibliography of American doctors and their writings, a bibliographical account of the medical periodical literature of the United States, a chronological list of medical periodicals in his own library covering the years 1797 to 1857, and a list of organizing members and Presidents and Vice-Presidents of the Medical Society of the State of New York.

Few physicians today have Dr. Purple's leisure or his devotion to the world of books, but the far reaching effects of his services to this Library can indicate to those interested in medical libraries or medical history, paths along which they might choose to follow.

The building of a useful collection, is of course only half the battle. The value of any collection can be judged solely by its use, and since the number actively interested in the history of medicine is small, the resources of the library of medical history are seldom fully utilized. The library can play a large part in stimulating the study of history, although discouragement may often be the reward. Statesmen, economists, lawyers, military strategists, must have knowledge of the history of their professions, but the majority of scientists feel that only the new is worthy of attention.

A few years ago an editorial in the bulletin of an English hospital noted that a recent gift was the only book on the history of medicine in the hospital library and remarked that it would be well to add a few more of the standard works and to introduce a few lectures on the subject. This mild suggestion provoked an immediate response in which the writer inveighed against investing "time and energy in a subject that did not give a profitable return." He said, "There can be no possible use in knowing anything about Bright or Addison or Lugol, nor in any of the

dilettante frills that so please those who possess them." This attitude is unfortunately shared by many, and the librarian who meets it frequently must wonder just how much time may be spared for such 'dilettante frills,' and how far he should go in trying to arouse interest in them.

It is obvious that those who are strongly against historical study are not apt to be influenced by any efforts in that direction, but there are those who, although they favor having an historical collection, feel that old volumes are merely curios or museum pieces, relics of an ignorant past. These and the medical students make up the audience that might be swayed, might profit by having historical material brought to their attention. As in advertising, "eye appeal" is surely the most successful bait. The man who passes unheeding by the carefully prepared exhibit which took hours of study and research, will pause before a small display arranged in a prominent spot with suitable illustrations and not too much text. New accessions may be shown, or descriptions of them mimeographed and circulated, such as Dr. McDaniel's informative and delightful "Fugitive Leaves." Recent gifts should receive proper publicity. Reprints of articles by members of the organization may awaken the interest of their colleagues. Accounts of the activities of other organizations may also provide incentive. Dr. Sigerist in his report of the activities of the Institute of the History of Medicine for 1943/44, describes their exhibits for that year. He lists three types: the scientific exhibits, the monthly student exhibits which correlated the history of medicine with current events, through such subjects as Salerno in medicine, Sicily in medicine, etc., and the book of the week exhibits which showed either a new book of particular interest, a new accession, or a publication of a member of the faculty. Every librarian cannot find the time for such a varied program, but surely some effort can be made in that direction.

The real work of the librarian, however, should begin with the new enthusiast.

² *St. Thomas Hospital Gazette*, 1940, vol. 38, pp. 59, 121.

Whether medical student or practising physician, the novice in the field of history is in need of assistance which the librarian can easily supply. The casual student may be satisfied with a few readable volumes. The serious student, and there will never be many, must go on from there. The first thing he must learn is the importance of original sources. He must be taught to consult them whenever they are available. He must be made to realize that no historian is infallible, that no source but the original is to be relied upon, that every fact must be documented, that every bibliographical reference must be clear, complete and specific, citing author, title, imprint, volume and page. Above all he must learn the necessity of accuracy. Dr Sarton writes, "The main point to emphasize is that accuracy is as fundamental in the historical field as in the scientific one, and that it has the same meaning in both fields. Most of the historical work done by scientists untrained as historians is published without means of verification, that is, with insufficient or imperfect references, and with so little accuracy that it is useless for later scholars."

Such work is obviously a waste of time for all concerned. It can add nothing to our knowledge.³ Dr Sarton does not add that later scholars may not be the only sufferers, for the historian himself may at a future date wish to check his sources. Then he must retrace his steps, a difficult and time-consuming chore after a lapse of time.

The next step for the beginner is to become familiar with the necessary reference tools. Here, too, the librarian can render the utmost service. For a rich heritage awaits the medical historian. History, biography, bibliography. In each field medical men have left enduring monuments. No subject has been more thoroughly covered. In the field of bibliography it is outstanding. In fact, the father of bibliography was a physician. The handsome folios containing Conrad Gessner's extraordinary work were published in 1545 and 1548. Today they

stand upon our shelves, not alone as a tribute to Gessner's industry, but also as useful books of reference. The *Bibliotheca universalis*, covering all existing literature, is no simple list of authors and titles, but an annotated catalogue often giving brief biographical notes, detailed contents, quotations from the authors' prefaces, the imprint, the number of chapters, and the source of his information. He may indicate that a volume was noted in Champier's *De scriptoribus medicinarum* or in Trithem's *Catalogus ecclesiasticorum scriptorum*, or he may mention the particular library in which he examined a copy of the book in question. Bibliographers of today can look with awe upon this tremendous compilation.

Gessner was succeeded by medical men of equal industry who confined their attention to the subject of medicine. Manget who brought out many large volumes in the early eighteenth century often quoted extensively from the original texts. Haller later in the century cited obscure texts and scarce editions overlooked by other bibliographers. Ploucquet in 1798-9 provided an extensive index of medical literature by subject, including references to case histories in the sixteenth century *Consilia* and to articles in the early scientific journals. In the years 1830 to 1845 appeared a thirty-three volume catalogue of recent medical publications, arranged by author and compiled by the Danish physician, Callisen.

These are but the most outstanding achievements in medical bibliography. There are many others over the centuries which make contributions to the subject. Together they comprise a vast amount of valuable material, material which has necessarily lost some of its glory in the shade of the work most vital to any medical library, the *Index-Catalogue*. Billings may be remembered as the last of the giants of medical bibliography, for through his efforts and those of his successors at the Army Medical Library no one need embark upon the impossible task of listing the ever increasing and voluminous mass of medical literature. Today bibliographers can limit

³ Sarton, G. A. L. *The study of the history of science*, Cambridge, Mass., 1936, pp. 10-11, 46.

themselves to subjects of less general scope, such as the detailed descriptions of editions of the writings of one author, so well exemplified in the books by Dr Keynes, Dr Fulton and Miss Doe, or of one specific subject, such as Schmid's bibliography of pathological anatomy

Medical history and biography have been no less well served. As Dr Malloch has pointed out⁴, it is only when the medical historian investigates subjects outside his particular field that he can appreciate the vast bibliographical and historical resources of his own. The novice may well be bemused and bewildered when he is faced with this literature for the first time, and the librarian is needed to show the way. Obviously no catalogue, however detailed, can offer adequate descriptions. The catalogue must be supplemented by the librarian's familiarity with the contents of his collection, by his intimate knowledge of the value of different volumes and by his imagination, a quality which should never be underestimated in historical research. Imagination and persistence are the most necessary qualities for both librarian and historian. Imagination can direct them to the less obvious sources where the needed information may lurk unsuspected. Persistence spurs them on when the discouragement of unsuccessful search fails to turn up a small but important detail. For the true historian realizes that history is but the amassing of one small fact after another, dull perhaps to the facile interpreter who is satisfied to base his calculations upon the work of others. But the historian knows that the discovery of any fact, no matter how insignificant, is an indisputable contribution. He knows, too, that the pursuit of such a fact may entail a chase as interesting as that of a detective in search of a criminal or the hunter in search of his prey. It is in guiding his initial steps along these lines that the librarian can best serve the historical collection.

In making plans for the post-war world we hear so much about, it is clear how the librarian can chart the proper course. The physician, too, can look ahead. It is to be hoped that in peace time more medical schools will offer courses in the history of medicine, or if not, that courses on various medical subjects may be introduced by historical summaries. Then the professor can urge his student to visit the historical collection, perhaps even to write a brief paper on some specific phase of the subject. The more specific his topic, the more will he learn, the more fully can he treat it. In this way, and with the librarian's help, the student becomes familiar with the historical books and their use.

Some method should be devised for the rousing of the physician as well as the student. A most profitable and workable solution might be the organization of a board of consultants, a board composed not of two or three men, but of a larger group, on whom the librarian could rely for occasional assistance. A physician might be selected from each medical specialty, one who had some interest in its history. The librarian would then be able to turn to members of this group when emergencies arose, and the men would surely feel active partners in the development and operation of the library. This is as it should be. I am sure that many physicians would be glad to give of their time and knowledge but hesitate lest the librarian resent intrusion or criticism, while the librarian often feels presumptuous at the thought of interrupting a busy man's practice.

The medical library exists for the medical man and he should learn that the more he contributes to it, the better it will serve him. The historian, completely dependent upon the library for his tools should be even more aware of this. Mutual effort on the part of physician and librarian can achieve our ideals, but neither one nor the other can succeed alone, and this should be given due thought in our many plans for the not too distant future.

⁴ *Bulletin of the Johns Hopkins Hospital* 1930, vol. 46, p. 61

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



APRIL 1945

THE DIVERSE CLINICAL PICTURE
OF CORONARY HEART DISEASE *

ROBERT L. LEVY

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WHEN, as the result of much study and discussion, the cardinal features of a clinical picture have been clearly defined, there comes a time when some of its less common aspects deserve mention. And often, after attention has been directed to these variants from the usual pattern, it appears that, after all, they are not such rare occurrences as was at first believed.

Coronary heart disease, in most cases the result of atherosclerosis of the coronary arteries, has indeed been a topic of widespread interest during the past quarter of a century. Its frequency has commanded respect. Many of its more dramatic symptoms are familiar not only to the physician but also to the well-informed layman. In stressing the diversity of its manifestations, I lay no claim to novelty. Examples such as those to be described and which serve as a basis for comment have, I am sure, been observed by many others.

In his book, titled "An Introduction to the Study of Physic," William Heberden,¹ better known for his classic description of angina

* Read at the Annual Meeting of The New York Academy of Medicine, January 4, 1945

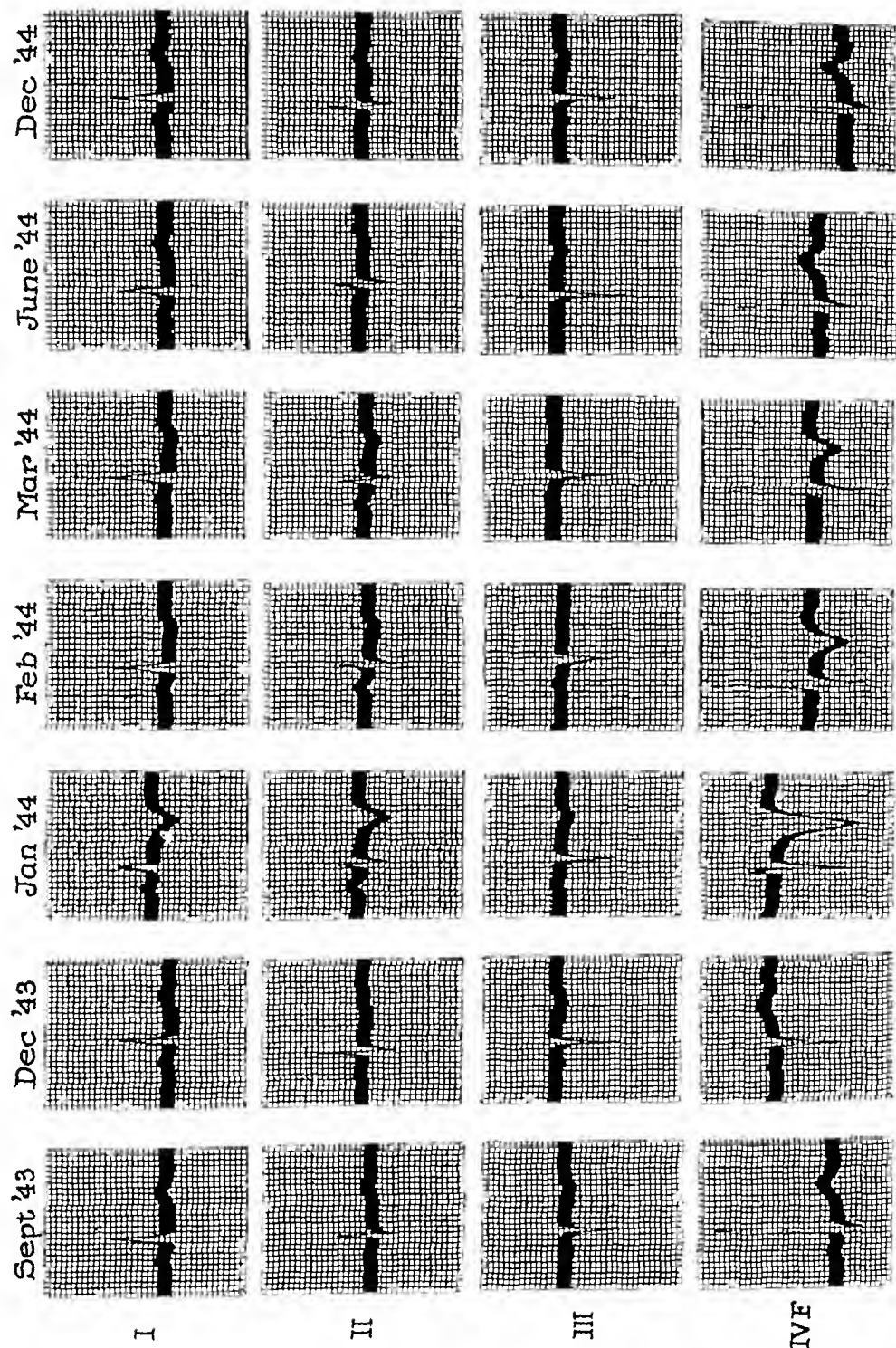


Fig 1-Case 1 Electrocardiograms of a woman, aged 71 years, with hypertension and mild symptoms. The alterations in the form of the complexes are striking

pectoris, offers this suggestion "Whoever would make a due use of his attendance on hospitals must be at the pains of writing down the history of diseases and the method of cure, that he may have a fair view of the case after it is ended, and to fix it deeper in his memory" It is with these simple aims in mind that the notes which follow have been compiled

CASE REPORTS AND COMMENTS

Case 1 Mrs A was first seen at the age of 67, four and a half years ago She had been remarkably healthy and led a pleasant, comfortable existence She had been aware of the presence of hypertension for eight years and for six months had noted palpitation when nervously upset.

Examination showed a small, slender woman with moderately marked retinal sclerosis The heart was not enlarged The sounds were of good quality and a faint systolic murmur was heard at the apex, as well as at the aortic area The blood pressure was 198/102 There were no signs of congestive failure The electrocardiogram showed left axis deviation, inversion of T 3, and an occasional auricular premature beat

The patient fared remarkably well for a period of three and a half years during which the systolic pressure ranged from 212 to 174, the diastolic, from 104 to 74 She led a normal life, avoiding undue exertion and taking an adequate amount of rest. On December 2nd, 1943, she returned to New York after having spent two weeks in Boston where she attended an operation performed on her sister Although not fatigued, she was aware of having gone through a trying experience The blood pressure then was 206/96 The electrocardiogram, for the first time, showed slight changes, in Lead 2 the T wave was inverted and in Lead 4F, R was small and S deep

On January 25th, 1944 (eight weeks later), she reported that she had been very tired after her Christmas shopping and had gone to bed for a week during which she had slight fever She called a physician who thought she might have a cold, but the patient herself was sure that she did not. There was no pain in the chest, her chief complaint was that she felt completely "done in" She was told that during this episode her blood pressure fell to 170 Since that time, she had had a good deal of aching pain in the left arm which she thought was rheumatic

The heart rate was 72, the rhythm was regular The blood pressure

was 202/96 Measurement of the transverse diameter of the heart in the orthodiagram showed an increase of a full centimeter compared to what it had been on December 2nd, 1943 The electrocardiogram showed striking changes, with deep inversion of the T wave in all leads (Fig 1) The leukocytes numbered 5,600, of which 62 per cent were polymorphonuclears The sedimentation rate of the erythrocytes (Westergren method) was 15 mm in one hour She was sent home and placed under nursing care

During the next three weeks she was kept in bed There was no discomfort in the chest at any time, nor was there any elevation of temperature The blood pressure was maintained at approximately the levels already noted During the first few days, the cardiac rhythm was irregular due to premature contractions At the end of four weeks she resumed her usual activities There have been no further upsets

There was a striking discrepancy between the mild symptomatology and the marked changes in the electrocardiograms Regression of the deformities in the complexes was slow but complete, and about seven months after the short febrile illness, the record resumed its previous form

Comment In this case, the electrocardiographic changes suggested a wide area of cardiac involvement, yet discomfort was slight and the patient was ambulatory for at least three weeks before she thought it worth while to report for examination It seems probable that one or more coronary branches became occluded without the formation of a large area of infarction Healing apparently was excellent

Inversion of the T wave in all of the three standard leads of the electrocardiogram is a relatively uncommon occurrence It is observed most frequently after acute coronary occlusion but may be found in a variety of other cardiac disorders A few instances have been noted in which there was no demonstrable heart disease In sixteen cases with this electrocardiographic pattern and symptoms of hypertension and coronary insufficiency during life, the heart was examined at autopsy by Barnes and Burchell² The usual findings were hypertrophy, severe coronary sclerosis and patchy fibrosis of the myocardium

Case 2 Mr B, a business man, aged 45 years, was first seen in July 1938, complaining of precordial pain and a heart murmur Both were first noted two years previously The pain was dull and often unrelated to exertion There was no radiation to either arm

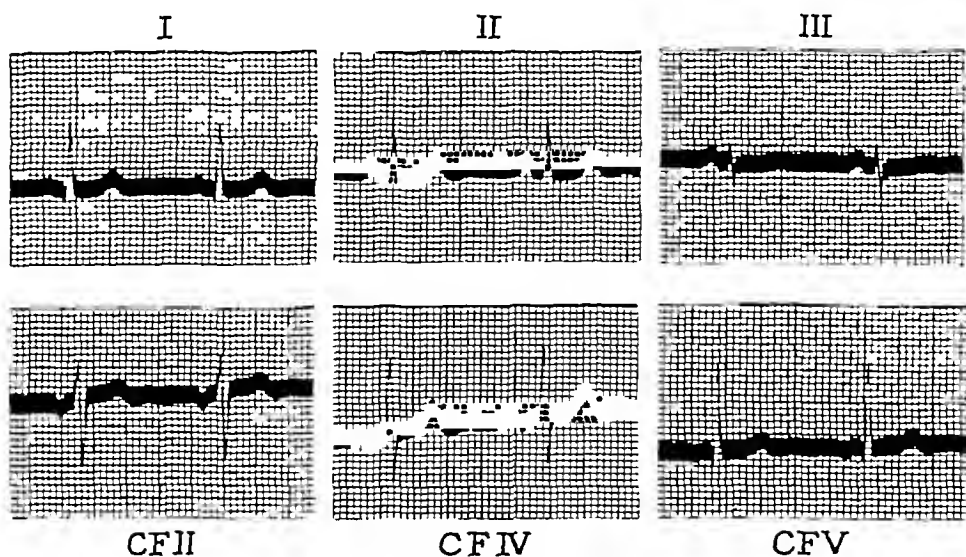


Fig 2-Case 2 Electrocardiogram of a man, aged 51 years. There is very slight concavity of the RS-T segments in Leads 1 and 2. Sudden death occurred one month later, as a result of fright.

Physical examination was negative. There was no retinal sclerosis. The heart sounds were clear. The blood pressure was 134/86. The electrocardiogram showed very slight concavity of the RS-T segments in Leads 1 and 2. He was obese and was advised to lose weight. He was asked to return if the symptoms persisted.

He was not seen again until October 11th, 1944, more than six years later. Apparently for two years after his first visit, he was quite well, then, four years ago, the pain returned with increasing severity and frequency. He could only walk one block without stopping to rest. Excitement at the race track caused the most intense discomfort. There was now radiation to the arms. He had not used nitroglycerin. Roentgenologic examination of the gall bladder, made several years previously, revealed sluggish emptying but no stones. He did not smoke and because liquor caused him to flush and made his heart beat rapidly, he took it rarely.

Examination showed a loss of sixteen pounds in weight in the past six years. The heart was not enlarged. The sounds were clear. The blood pressure was 128/84. The electrocardiogram showed left axis deviation and again, very slight concavity of the RS-T segments in Leads 1 and 2 (Fig 2). The record was similar to the one taken at the time of his first visit.

It seemed clear that this man's discomfort was due to coronary insufficiency and a suitable regimen of activity and rest was outlined.

Exactly one month later, the patient's death was reported in the newspapers. His body, fully clothed, was found on his bed, where also lay his wife's jewel case. This had been forced open and several of the larger pieces of jewelry were missing. In the living room of the apartment, drawers of desks had been pulled out and the contents scattered about the room. The liquor cabinet had been opened and two bottles were lying on the floor. Chairs on the terrace had been overturned. According to the New York Times, while the police were trying to determine the facts, the detective captain in charge stated that "Mr B may have come home and seen a burglar or evidence of a burglary and probably suffered a heart attack." Apparently this is precisely what happened.

The essential findings at autopsy were supplied through the courtesy of Deputy Chief Medical Examiner B M Vance. There was no evidence of external violence. The heart was not enlarged. There was marked sclerosis of both coronary arteries with calcification and extreme narrowing of the main branches. The myocardium showed patches of fibrosis. There was neither recent thrombosis nor cardiac infarction.

Comment This is an instance of acute, fatal coronary insufficiency in which sudden death followed an intense emotional experience.³ The lack of important signs of coronary heart disease during life is noteworthy although the symptoms were characteristic. This man literally was "scared to death."

Case 3 Mr C, age 73, gave a story of substernal pain for three years. This occurred on walking in the wind or after a meal and disappeared promptly on standing still. He had never taken nitroglycerin for relief. One week before his visit, after breakfast, he had a more severe pain than usual which persisted for about two hours. There was no radiation to the arms. On the morning of his visit, he had a similar pain, also lasting for several hours, this had not entirely disappeared when he presented himself for examination.

There was slight retinal sclerosis. The heart was normal in size on percussion. The sounds were distant and the first sound at the apex was reduplicated. The blood pressure was 126/68, which he stated was his usual level. Fluoroscopic examination and an orthodiagraphic

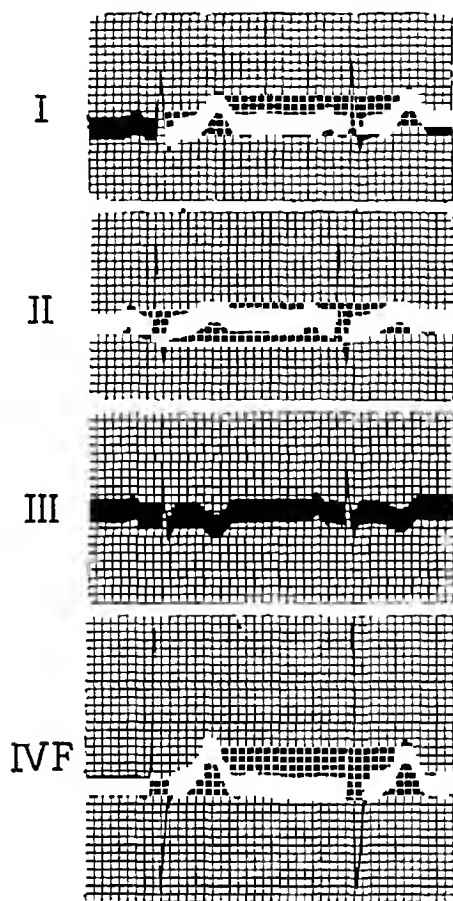


Fig 3-Case 3 Electrocardiogram of a man, aged 73 years
The record is within the range of normal He died twenty-three hours later of acute coronary occlusion

tracing showed no cardiac enlargement but the left ventricle was full and rounded The electrocardiogram (Fig 3) showed no significant changes The erythrocyte sedimentation rate was 13 mm in one hour (Westergren method)

The patient was advised to go home to bed He felt so well that he walked several blocks to a druggist's shop to fill a prescription

After a comfortable night, the pain recurred at noon on the next day It was persistent and increased in severity A state of shock soon developed and he died two hours later and twenty-three hours after the electrocardiogram was taken Although an autopsy was not performed, it seemed clear that occlusion of a large coronary branch was responsible for the terminal episode

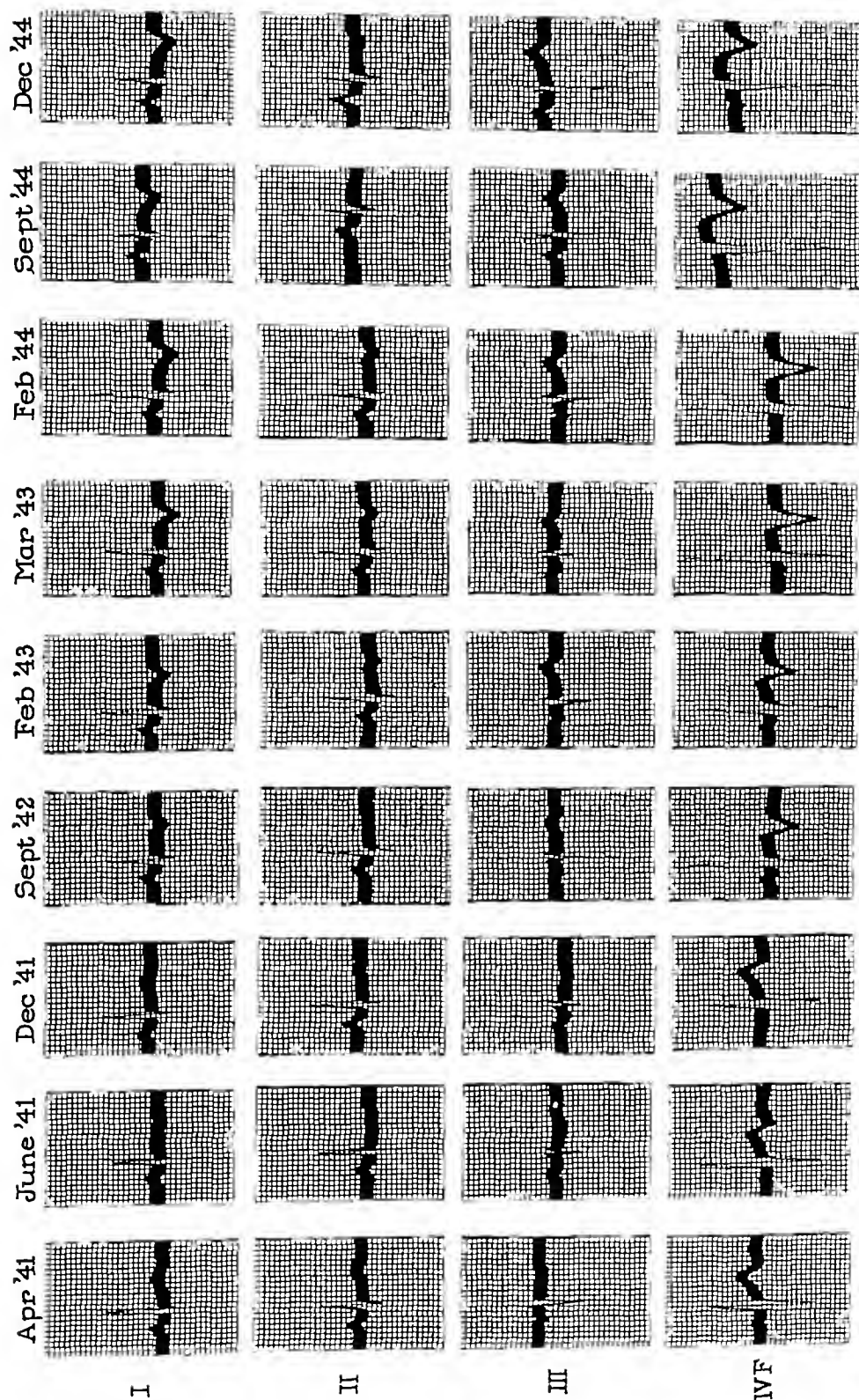


Fig 4-Case 4 Series of electrocardiograms of a man, aged 60 years when first seen. There are frequent and marked changes in form, but throughout this period of three and a half years, he has been active and entirely free from discomfort.

Comment In this case, it is probable that actively progressive changes were taking place in a coronary artery for at least a week. In spite of this fact the electrocardiogram, taken less than twenty-four hours before death, afforded no clue to the impending closure.

Case 4 Mr. D., a lawyer, was first seen at the age of 60 in March 1941. There were no symptoms referable to the heart. He had recently been in a hospital for hemorrhoidectomy and at that time, an elevation of blood pressure was first noted. For this reason, he was referred for more complete examination.

There was moderate retinal sclerosis. The heart rate was 76, the rhythm was regular. The sounds were strong and clear. The blood pressure was 182/106. The electrocardiogram showed slight left axis deviation but was otherwise not remarkable. Measurement of the orthodiagram showed enlargement of the heart, chiefly to the left, and moderate, diffuse dilatation of the aorta.

The patient was seen at frequent intervals during the next three and a half years. He never had discomfort of any sort. He continued as a practising lawyer but shortened his hours of work and rested for an hour each day after lunch. He played golf regularly, both at home in the summer and in Florida in the winter. He danced moderately. In June 1944, he recovered from an attack of primary atypical pneumonia without any cardiac disturbance.

The series of electrocardiograms pictured in Fig. 4, shows changes which, taken by themselves, would lead to the belief that lesions of serious consequence had occurred in the heart. Certainly there were occlusions in the coronary bed, but these apparently developed gradually and in the presence of an adequate collateral circulation. At no time was there an increase in the sedimentation rate of the erythrocytes or any fall in blood pressure.

This patient was last seen on December 12th, 1944. He considered himself unusually well. The first sound at the apex was reduplicated and was followed by a short systolic murmur. The blood pressure was 164/114. The size of the heart was the same as in March 1941.

Comment These striking electrocardiographic changes occurred in an elderly man with hypertension who, throughout the period of over three years during which they were observed, led an active professional life, danced and played golf. He was entirely free from discomfort. I confess that at times I was somewhat concerned about the wisdom of

sanctioning this regimen Yet there did not seem to be sufficient reason to advise that he relinquish the interests and relaxations which he enjoyed, and I know that he preferred to assume whatever risk was involved rather than to live on a lower plane of activity It is questionable whether he would now be any better off had he retired and rested, I doubt it How long such a series of insults may be continued without symptomatic evidence of cardiac damage, will depend upon the balance between the amount of obstruction and the extent of the collaterals in the coronary bed

If electrocardiograms are taken at frequent intervals in patients with coronary sclerosis, it is not uncommon to discover varying patterns without associated symptoms Such an occurrence need not occasion surprise, for it is in accord with the concept that arterial degeneration is inherently a progressive process The changes are not always as marked as in this case But even several main coronary arteries may be occluded before the final illness, in the absence of anginal pain or congestive failure This has been clearly demonstrated by Blumgart and his associates,⁴ who correlated the clinical manifestations with the pathologic lesions in hearts injected and dissected at autopsy

Case 5 Mr E was a manufacturer, 59 years of age He complained of substernal pain One brother died at 69 of cardiac disease, and one sister, who was living at the age of 71, had suffered from an attack of coronary thrombosis eighteen months previously The patient had been treated for peptic ulcer nine years earlier, with relief of symptoms and apparent healing of the ulcer Twenty months before I saw him, he had a tarry stool which was ascribed to bleeding from a small erosion of the gastric mucosa This had healed

The present discomfort began six weeks before his visit, with substernal pressure which occurred chiefly at night Four weeks before, while playing cards, he first felt severe pain, lasting five minutes, and that same night, had further discomfort lasting a half hour He was put to bed for four days and remained at home for a week following There was some improvement but he still complained of nocturnal and early morning discomfort Nitroglycerin gave prompt relief There was no radiation of the pain but he experienced tingling in the left arm with the sharper attacks He rarely smoked and drank liquor infrequently He had continued at his business

Examination showed well marked retinal sclerosis The heart was

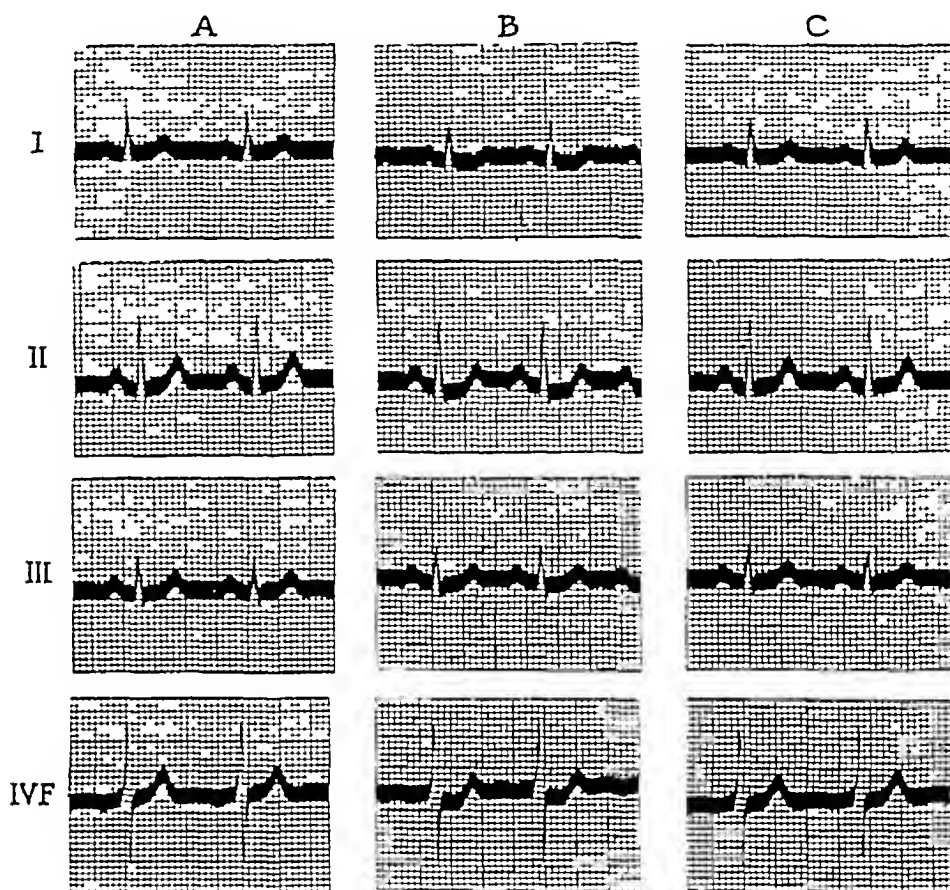


Fig 5—Case 5 Anoxemia test of a man, aged 59 years, with pain in the chest and a peptic ulcer A, control B, after breathing 10 per cent oxygen for twenty minutes C, after breathing 100 per cent oxygen for two minutes The test is positive. Depression of the RS-T segments, apparent in B, disappears promptly after inhalation of pure oxygen

not enlarged, either on percussion or on roentgenologic examination. The rhythm was regular, the rate was 80. The sounds were moderate and no gallop was heard. There was a faint systolic murmur at the apex. The blood pressure was 144/78. The electrocardiogram was normal and was similar to those previously taken over a period of years.

In spite of the absence of clinical signs of coronary heart disease, it seemed probable that the patient's pain was due to coronary insufficiency. Because of his gastric history, it was suggested that roentgenologic examination of the gastro-intestinal tract be repeated. This was done and an active duodenal ulcer was found. There was no hiatus hernia. The consulting gastro-enterologist was of the opinion that dis-

comfort could be explained on the basis of the lesion in the digestive tract

The patient's physician, however, was not satisfied with this interpretation and at his suggestion, Mr E returned for an anoxemia test. This was positive, as shown in Fig 5. The changes were particularly evident in the RS-T segments. The sum of the deviations in the four leads totalled 3 mm. According to the criteria now employed, this is a sign of a positive test and indicates coronary insufficiency. The patient was able to breathe the 10 per cent oxygen mixture for twenty minutes but complained of slight substernal pressure during the last two minutes of the test. After breathing 100 per cent oxygen for two minutes, the changes in the electrocardiogram caused by anoxia were abolished.

Comment The clinical picture in this case was confused by the presence of a peptic ulcer and the absence of definite signs of coronary heart disease. The anoxemia test afforded graphic evidence of coronary insufficiency.

THE ANOXEMIA TEST IN DIAGNOSIS

Not infrequently it is difficult to determine the source of discomfort in the chest, particularly when the patient complains of pain. Such discomfort may be due to various causes originating at a distance from the point of reference. Among conditions which sometimes cause confusion are gall stones, hiatus hernia, esophageal spasm, arthritis of the spine and a psychoneurotic state. Several procedures have been suggested to increase the work of the heart under conditions which make it possible to determine, indirectly, a diminution in coronary reserve. In the Department of Cardiology at the Presbyterian Hospital, we have been particularly concerned with the development of the anoxemia test^{5, 6}

This consists of permitting the patient to breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or until cardiac pain appears. A control electrocardiogram is taken and records are made at intervals of five minutes while the patient breathes the low oxygen mixture. Measurement of these records shows, in patients with a diminished coronary reserve, characteristic changes which are not observed when the coronary blood flow is adequate. Based on analysis of a large experience, criteria have been evolved which are regarded as evidence of a positive test.⁷ The result is positive when any one of the

following is found

- 1 The arithmetic sum of the RS-T deviations in the four leads employed (I, 2, 3 and 4F) totals 3 mm or more
- 2 There is partial or complete reversal of the T wave in Lead 1, accompanied by an RS-T deviation of 1 mm or more in this lead
- 3 There is complete reversal of the direction of the T wave in Lead 4F, regardless of any associated RS-T deviation in this lead

The occurrence of pain during a test which is electrocardiographically negative is considered *presumptive* evidence of coronary insufficiency. In this event, the patient should be carefully watched for further signs of coronary disease and managed conservatively. Often such signs later make their appearance, and frequently the anoxemia test subsequently yields a positive result.

If carried out according to directions, the test is simple and safe. It has been found useful in differential diagnosis, both in our experience and that of others.^{1,9} If three fundamental precautions are observed, serious reactions are avoided. The test should not be performed under the following circumstances: (1) in the presence of congestive heart failure, (2) within four months after known cardiac infarction, (3) on the same patient more than once in twenty-four hours. A positive test indicates a diminished coronary reserve but gives no information as to the nature and extent of the pathologic lesions in the heart. A negative result does not rule out the presence of disease of the coronary arteries, for, as in any functional test, there must be a significant decrease in reserve before insufficiency can be demonstrated.

SUMMARY

Attention has been directed to some of the less common clinical aspects of coronary heart disease. There may be minimal symptoms and marked changes in the form of the electrocardiogram. In the presence of advanced coronary sclerosis, a severe emotional strain can induce acute coronary insufficiency and so cause sudden death. The electrocardiogram may be normal less than twenty-four hours before fatal coronary occlusion. There may be striking serial changes in the electrocardiogram indicating closure of coronary arteries in a patient who is ambulatory, active and entirely free from cardiac discomfort. When the symptoms are puzzling and the examination including the electrocardiogram reveals no signs of heart disease, the anoxemia test is often useful in affording graphic evidence of a diminished coronary reserve.

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THE TREATMENT OF CORONARY
DISEASE *

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I WAS with reluctance and misgiving that I accepted the flattering invitation of your Committee to discuss the treatment of coronary disease. We all know that progress in this field, despite much hard work, has been modest and that we have little more than a toe-hold on the problems which beset us. Moreover the therapy of coronary disease has been discussed so frequently that one hesitates to add still another presentation to a literature whose volume is already out of proportion to knowledge of the subject. I could not cover all aspects of the topic assigned me in a presentation of this length. I have no startling new facts to bring to your attention. At most I can share with you certain of my reflections and points of view that have developed in the course of struggling with this problem for many years.

INVESTIGATIVE STANDARDS AND OBJECTIVES

The charge that its investigative work is not on a high plane has frequently been leveled against clinical medicine. The most recent of such criticisms to come to my attention is contained in the following quotation from Sir Thomas Lewis ¹ "Clearly to recognize the limitations of present day knowledge and fully to realize the contrast between medical writings and the closely reasoned argument and precise recording now found in the ancillary sciences, are matters of prime consequence in an approach to the problem of reform in medical education." One need not necessarily be so impressed as is Sir Thomas by the contrast between "medical writings" and those of the "ancillary sciences" but the need for closely reasoned argument and precise recording in all scientific fields can scarcely be challenged. One might add that the closely reasoned argument requires tests of the assumptions upon which

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it is based as well as careful checking at every step by precise recording, otherwise, even those working in the ancillary sciences such as the physiologists may stray from the path of truth. I venture to assert that there are many clinical investigators whose work is fully up to the standard of the best produced by their confreres in physiology. On the other hand we have to admit that much of what is published in the clinical journals and books does not stem from that vitally essential combination of closely reasoned argument and precise recording. Too much of the literature dealing with coronary disease is open to this criticism, so much in fact that it constitutes a handicap to those trying to educate themselves and a burden to all who wish to keep abreast of current developments.

Advances in the treatment of coronary disease may result from the discovery of new and more effective procedures or from careful studies which demonstrate more clearly the indications and best methods of use of measures now available. The most urgent needs however are (1) improvement in diagnostic methods so that we can recognize the disease in a far earlier stage than at present and (2) more accurate and complete knowledge of the etiological factors concerned in its production.

THE UNSATISFACTORY STATUS OF ETIOLOGY

The difficulties which beset investigation of the causes of coronary disease could scarcely be overestimated. Because in the vast majority of cases it is a manifestation of atherosclerosis, it has been widely assumed that its causes are identical with those of atherosclerosis of other vessels. Such an assumption seems reasonable but it does not take into account possible causes of relatively early and extensive involvement of coronary arteries, as compared with certain other parts of the arterial tree, observed in some individuals. Experimental work seems to show that by certain procedures the coronary arteries can be acutely damaged without material involvement of other arteries.² Such results make it seem not unreasonable to entertain the idea that in humans certain etiological factors may produce selectively more atherosclerosis of coronary arteries than of other vessels. Dock³ has suggested that their relatively thick intima may make these arteries vulnerable.

It seems to be assumed by most writers on the subject of coronary disease that not only is its incidence on the increase but that certain disorders dependent upon it such as angina pectoris and acute coronary

occlusion are increasing even more rapidly. Unfortunately we lack the "precise recording" by which such questions can be settled. Cohn and Lingg⁴ in 1934 could not obtain evidence from comparative studies of vital statistics to indicate that coronary disease, taking into account "fashions in diagnosis" and lessened mortality in youth, was much more common than it had been thirty years before. There is no yardstick by which the comparative frequency of angina pectoris and acute coronary occlusion can be measured. One is impelled almost irresistibly to the conclusion that these conditions are more common to-day than they were in the past but evidence to establish that view is lacking. Although most of us knew nothing about acute coronary occlusion thirty years ago, the newspapers of that day featured the sudden death of prominent members of the community just about as frequently as they do now. I still recall the statement of the late Edward Martin made to his class in surgery in 1910 that nearly all of the sudden deaths reported in the newspapers as acute indigestion were in reality due to heart disease.

It would be very helpful if we could settle the question of the relative frequency of coronary disease or any of its manifestations today and in the past. If long familiarity with the assumption that they are increasing and frequent assertion of it make us believe that assumption to be established and we base further work on such a belief without holding it under question, we depart from the scientific method. Acceptance of untested but frequently repeated assumptions is undoubtedly one of the major causes of error in human reasoning. As one examines the upper range of the scale of intellectual sophistication, the traps for the unwary merely become harder to detect. The literature of medicine abounds with them even today. A classical example which does not leave untouched some of our colleagues in the "ancillary sciences" is the history of the Einthoven equilateral triangle hypothesis. This hypothesis constructed by erecting assumption upon assumption without testing most of them, has been used for over thirty years as the starting point for further research leading to voluminous literature. If even one of the important assumptions which underlie the famous hypothesis is shown to be invalid, as I believe it has been, this enormous superstructure falls like a house of cards and thirty years of work along certain lines will have proven a total loss. In view of the many untested assumptions regarding the causes of coronary disease which receive widespread acceptance I believe we are in danger of perpetuating major error in our

thinking and in our work on that subject and above all in our management of patients

I shall offer only one illustration of the point I have tried to make above and select it because of its bearing on treatment. Many, including myself, believe that certain manifestations of coronary disease such as angina pectoris and acute coronary occlusion are much more common at relatively early ages in heavy smokers than in the general population. One can scarcely fail to be impressed by the large proportion of patients under the age of forty with such disorders who smoke cigars or cigarettes in great excess.⁵ It is therefore tempting to conclude that tobacco has been responsible for the coronary disease and its consequences found in these relatively youthful patients. Moreover such a view is supported by other facts. The effect of tobacco in producing vasospasm in peripheral vessels has been demonstrated. Changes in the electrocardiogram can sometimes be produced and occasionally anginal attacks can be precipitated by smoking one or two cigarettes. The frequency of anginal attacks sometimes seems to be lessened if the use of tobacco is stopped. Such an array of evidence seems convincing. On the other hand, there are many heavy smokers who never develop any evidences of coronary disease, probably a far larger group than those who do. There are many other heavy smokers with angina pectoris who are not improved to any perceptible extent by stopping the use of tobacco. Finally one must ask himself to what extent it may be the restlessness, lack of self-discipline or whatever it is that makes some individuals heavy smokers, that is responsible for the coronary disease rather than the tobacco itself. Should we then on the basis of such an unproven case try to stop our patients with coronary disease from smoking? It is asking a lot of a man who is restricted in so many other ways to give up the solace of tobacco. It would seem unwise, however, to advise patients with frequently recurring anginal attacks to continue the use of tobacco without giving abstinence from it a fair trial, whether or not its use accelerates the progress of pathological changes in their arteries. In general it has seemed to me that patients with coronary disease who stop smoking do better than their less cooperative friends but perhaps this is because they follow all their orders better. We still have before us the task of proving that the use of tobacco tends to bring on coronary disease or shortens the life of its victims.

It may be found some day that there is one vital essential link in

the chain of developments leading to the production of atherosclerosis, just as has proved to be the case in the formerly equally mysterious pernicious anemia. In the latter the discovery of effective treatment antedated knowledge of etiology of the disease and actually led to it. However, pending such a happy development in the case of coronary disease we may attempt in so far as it is possible with our limited knowledge to utilize the method of multiple working hypotheses, assuming in each case the probability that a number of factors are operating more or less concurrently.

In view of the frequency of coronary disease and our inability to recognize it until it reaches an advanced stage in at least one or more places in the coronary arterial tree, I think we should assume that any man approaching the age of fifty may have the beginnings of coronary disease, no matter how healthy and vigorous he appears to be. Thus, when a presumably healthy individual of middle age or beyond asks what he can do to keep from getting heart disease, one can at least advise him to be moderate in all things. Obviously if there is a family tendency toward conditions known to accelerate the development of atherosclerosis such as diabetes or hypertension, special emphasis should be placed on examinations for such conditions in order to discover them in an early stage.

PERIODIC OR HEALTH EXAMINATIONS

The rapidly increasing emphasis on preventive medicine and growing acceptance of periodic or health examinations by industrial organizations and by individuals present an ever greater problem to physicians concerned with the cardiovascular aspects of these examinations. Some papers advocating such examinations overestimate the ability of physicians to detect coronary disease in its early stages and to retard its further development. Too many who have been slapped heartily on the back and told they have no heart disease have died during the next few days or weeks, to the discredit of their optimistic examiners. The most one is justified in saying after a negative examination is that no evidence of heart disease has been found. On the other hand too many are told that they have heart disease on the basis of findings that do not actually establish the fact. In the past such a finding was often an innocent murmur, now it is apt to be some deviation from empirically derived electrocardiographic standards which do not deserve all the faith sometimes

reposed in them. The greatest problem of all concerns the far from small percentage of individuals in older age ranges who present unmistakable evidence of myocardial involvement, in some the result of hypertension but in many others coronary disease without hypertension. Perhaps the greatest single mistake made in the management of these groups is to assume that prognostic data obtained from the study of patients who seek medical advice because of illness apply with equal force to those who are without symptoms. For example bundle branch block in hospital practice has in general an ominous prognosis although there are many exceptions to the rule. On the other hand bundle branch block found in examinations of the presumably healthy has a far more favorable outlook. These individuals as well as others found to have evidence of coronary disease should be instructed to avoid strenuous physical activity, to obtain adequate rest and sleep and avoid indiscretions of food intake and intemperance in other habits. Those whose duties entail severe physical or mental strain should be advised to try to obtain easier work. However, care should be exercised not to place unnecessary restrictions on the lives of these men, and above all not to stop them from useful work if they are able to carry on, and wish to do so. Otherwise one may engender a sense of defeat, mental depression or anxiety. Individuals unnecessarily restricted like those who receive a mistaken diagnosis of heart disease would have been far better off without health examinations.

GENERAL CONSIDERATIONS IN THE TREATMENT OF PATIENTS

The evaluation of treatment in coronary disease is made difficult by the unpredictability of events in any individual case. Studies of the course of the disease have been attempted by many investigators. While the results have not always shown close agreement, they have nevertheless given us figures that enable one to predict with some approach to accuracy, the percentages of complications and the mean expectation of life for large groups of cases. However, to predict what will happen to one patient is sheer guesswork. Everyone familiar with this disease knows that some of the patients desperately ill with acute coronary occlusion not only survive but eventually make a remarkably good recovery and live for many years. Conversely a patient with an apparently mild seizure may die or if he recovers, remain a cardiac cripple as long as he lives. The patient in whom the disease has progressed only to the

point where it can be recognized, may rapidly grow worse or the disease may remain no more than a slight handicap to him for many years. Even those with findings which indicate that coronary disease has gone far enough to produce extensive changes in the myocardium, may have no symptoms whatever and remain active indefinitely.

Even though at present we have no accurate idea as to how much the things we do prolong the lives of our patients with coronary disease or retard the progress of their disease, one need not feel pessimistic about advances along these lines in the future. We have already learned that the problems are not simple and that they cannot be solved by crude investigative methods. Whether or not we discover the vital link or links in the causation of atherosclerosis, there is little doubt that "closely reasoned argument" and "precise recording" can solve some of the problems of treatment. However, in spite of what has been said above, we can do many things to make the lives of our patients more comfortable and useful and we can protect them to some extent at least from unnecessary disabling illness or sacrifice of their lives.

In this day of specialization it is not uncommon to find a patient under treatment by specialists in various fields independently of each other, reminding one of Stephen Leacock's hero who jumped on his horse and rode off in every direction. In group medicine this evil is avoided to some extent at least by a coordinator. In the ordinary practice of medicine it is the general practitioner who should be the coordinator in cases complex enough to require study by others. Patients should be educated to come to him rather than seek out specialists to examine them for what they think is wrong. He is the one who should decide whether special studies are necessary and also to whom the patient should be sent. Treatment unless of a type requiring special skill or equipment or both should be carried out under his direction.

To use an old medical cliché and say that the treatment of coronary disease must be individualized is almost an understatement. This rule applies to almost everything we try to do for these patients. The passion for standardization of all things that can be standardized has led to certain practices in the treatment of coronary disease that can scarcely be defended on rational grounds. One of these is the dictum that every patient who has had an acute coronary seizure should spend four to six weeks at complete bed rest. We owe a debt of gratitude to those who have led the recent revolt against unnecessarily prolonged

bed rest. Not the least of their accomplishments is to help free physicians from bondage to rules, violation of which has made them subject to criticism for any one of the unpredictable events that may occur at any time in patients with advanced coronary disease. No one at this time knows enough about coronary disease to make dogmatic statements about the grade and duration of rest that would prove best for each patient.

The mental and emotional aspects of coronary disease should never be lost sight of in treatment. The publicity accorded this disease and its manifestations in the lay press, the constant emphasis placed on the possibility of sudden death and the fact that almost everyone has personal knowledge of cases in which sudden death or permanent invalidism has occurred, have engendered fear of coronary disease in those who think they may have it that is apt to complicate treatment. All physicians of experience in this field have seen patients incapacitated from fancied heart disease who have recovered as soon as they were actually convinced that they did not have it. We are inclined to pay more attention to the psychiatric state of those who exhibit their neurosis in plain sight. We may however neglect the mental and emotional reactions of those who do not place them on parade but which nevertheless may have a definite bearing on their symptoms.

One of the most interesting aspects of the influence of mental and emotional factors on the symptomatology of coronary disease may be seen in those who hold total and permanent disability insurance policies. Even after seizures that would be classified on the basis of objective evidence as slight, the prognosis for recovery sufficient to enable them to return to work seems to be far worse than in the case of non-policy holders. The physician who helps his already apprehensive patients increase their fears incurs the risk of prolonging incapacity. It is only the incurable optimists who think nothing can happen to them and therefore fail to cooperate in treatment who are benefitted by stimulating respect for their disease.

Advice to a patient as to rest and activities which fails to take into account his psychology because of concentration on the purely physical aspects of the condition may not turn out as well as one anticipates. The physician should be prepared to compromise between the two and make further adjustments depending on the course of events. In general it has seemed to me far better to permit the victims of coronary disease

to carry on useful even though somewhat restricted lives and even permit recreations that do not tax their hearts too much than to have them slowly disintegrate both physically and mentally in an easy chair I venture this assertion fully cognizant of the fact that occasionally patients subject to angina pectoris may develop an attack on exertion which instead of subsiding, continues with the development of acute coronary occlusion and myocardial infarction

INTER-RELATIONSHIPS WITH OTHER DISEASES

The attempt to correlate all of a patient's symptoms under a single diagnosis has long been regarded as sound in principle. It has not, however, so far as I am aware, been sufficiently emphasized that this principle applies with most force to acute illnesses. In diseases as chronic as coronary disease we have to recognize the fact that some of the symptoms of which a patient complains may arise from another of the various disorders to which human flesh is heir. We have also to consider the influence of each of these disorders on the symptoms of the other. I shall mention only a few of these inter-relationships which seem to me important from the viewpoint of treatment although a fairly extensive list might be prepared. The fact that anemia or hyperthyroidism may aggravate or even precipitate the anginal syndrome or heart failure in patients with coronary disease is well known. Under these circumstances the most effective treatment of the cardiac symptoms is control of the anemia or hyperthyroidism. Pains referred along the brachial plexus or intercostal nerves from non-cardiac causes in cases with coronary disease with or without the anginal syndrome, are apt to cause mental anguish to a patient. If he knows he has heart disease it is difficult to convince him that most of the pains around his heart and down his left arm are not caused by his heart disease. The interrelations of symptoms of gall bladder disease and heart disease are often difficult and sometimes impossible to unravel completely. It may be a nice question to decide whether the gall bladder should be removed. In my experience the anginal syndrome has been relieved in only a relatively small percentage of patients with co-existing gall bladder disease. Thus, in considering operation one must give weight to the added risk because of heart disease and should not have too much confidence that the cardiac symptoms will be improved, although symptoms due to digestive tract disturbance which may simulate anginal pain may be completely relieved.

Perhaps the most confusing of all situations arises when painful esophageal spasm occurs in patients who are also subject to the anginal syndrome because the location and type of distress in the two conditions may be similar. Such a case was reported by Edeiken⁶ and we have seen several since that time. Misinterpretation of painful episodes of esophageal spasm as manifestations of coronary disease may intensify the agitation at least partly responsible for their production and make treatment futile.

Emphasis on the principles of treatment of coronary disease discussed above is tantamount to an admission that more direct methods of attacking it are limited in their effectiveness. If we learned how to reverse or even to check the atherosclerotic process, methods of doing so would become the most important thing to talk about.

DIET

Many workers feel that atherosclerosis is essentially the result of a metabolic fault and some go so far as to point to cholesterol as the cause of the trouble, particularly the excessive intake of cholesterol of animal origin. Data obtained from animal experiments and an array of clinical observations can be used to support this view. If or when convincing evidence can be presented that low intake of animal cholesterol prevents the occurrence of coronary atherosclerosis or retards its further development, I believe we will be able to convince some of our patients to eat foods with low animal cholesterol content. We would not even have to bother much about women unless they were already hypertensive or diabetic because of the relative immunity of the remainder to coronary disease. It should be a far easier matter to obtain the cooperation of patients in limiting cholesterol intake than in the painful process of reducing their caloric intake enough to lose weight. It would therefore be difficult to overestimate the importance of proving just what part cholesterol or anything else we ingest plays in the development of atherosclerosis. Everyone who has had experience in necropsy work in China agrees that atherosclerosis is rarely found in the aortas or coronary arteries of the Chinese. It might eventually save thousands of American lives every year, including members of the armed forces if lend lease funds could be allocated to feed enough Chinese over a long enough period of time, diets high in animal cholesterol content such as many Americans use from choice in order to find out

whether their metabolism is superior to ours or whether they are merely more sensible about what they eat. Possibly also careful studies during the next few years in Europe on those whose intake of animal cholesterol has been low almost from the beginning of the present war will yield information of value. It would be most instructive to find out whether those who emphasize the value of such foods as milk, butter and eggs to growing children are laying the foundations for coronary atherosclerosis and are thus unwittingly responsible for premature death in the future of up to 25 per cent of the children whose parents are persuaded to use the diets recommended. If coronary disease is actually more common in the United States than it was a few generations ago it is by no means improbable that changes in diet are at least to some extent at fault, and perhaps not those changes which are most criticized. We must have these questions answered: (1) Is coronary disease caused by a fault in metabolism? (2) Is it caused by excessive intake of cholesterol? (3) Is it caused by a combination of the two factors operating in the same individual? (4) Are none of the above concerned in its production? In formulating diets for patients with the idea of preventing coronary disease, without the answers to these questions we are in the same position as those who solemnly tell us what is good for us to eat. I do not mean to imply that we have not learned much about the use of diet in the treatment of certain diseases nor that the knowledge gained has not been of great value. However, the time has come when we must lift our sights and be concerned with the more remote and therefore less easily discovered effects of special diets. We have already had a good lesson on this subject when it was discovered that the high fat diet for diabetics in pre-insulin days, although it seemed to help the diabetic state at the time, was followed by a much greater incidence of premature atherosclerosis than we now encounter in diabetics. However we do not know what a high fat diet will do to the arteries of non-diabetics.

Physicians have to give advice regarding diet to nearly every patient with coronary disease. If they should be so remiss as to forget it, the patients or their families will almost certainly inquire about it. We all know that these individuals should not overload their stomachs, select foods calculated to test the limits of their digestive capacity, eat a large meal just before going to bed, or starting a golf game, or try to drink all the fluids they can hold because health columnists have said this is a

good thing to do. A marked dietary indiscretion or gastro-intestinal upset may precipitate an attack of acute coronary occlusion in those in whom the stage is set for such a calamity. That the gastro-intestinal tract is liable to become the temperamental *prima donna* of coronary disease in its more advanced stages is only too well known to everyone who has to treat some of its victims. I have no better explanation for this than anyone else who has discussed it, no new suggestions for diverting patients from concentration on their gastro-intestinal tracts and no additions to propose to the present list of relatively ineffective remedies. It has seemed to me that after other causes of digestive disturbances have been ruled out as completely as possible, psychotherapy with attempts to convince the patient that there is no actual disease of the digestive tract and that his indigestion is the result of disturbance in nervous control of that tract may sometimes help more than medication. These patients by abstaining from one food after another in the effort to obtain relief may bring on themselves deficiency states which may actually aggravate their digestive disturbances.

Life insurance statistics have made it clear that obesity after youth carries the penalty of decreased expectation of life. It is not clear, however, whether this is the result of obesity *per se* or other effects of a possible metabolic fault responsible for obesity despite the fact that those constitutionally slender are apt to regard all obesity as exogenous. There can be little doubt that some of the obese feel better after diet and loss of weight. They are less breathless, gastro-intestinal symptoms may improve and even anginal pains, if they are subject to this disorder, are less easily evoked. Others, however, feel weak and unhappy when placed on a diet. It is not unusual to obtain a history from patients who have been persuaded to lose a lot of weight merely because they were too fat, that loss of weight marked the beginning of illness. Some excessively obese cardiac patients rapidly deteriorate and die of heart failure when placed on drastic reducing diets. Moreover, the frequency of acute coronary occlusion during or shortly after marked loss of weight is such as to raise a question whether this is purely coincidence. While slow weight reduction is doubtless highly beneficial in many, one should probably not try to make all have figures like debutantes.

MEDICINAL TREATMENT

Most patients when they visit a physician hope that he will be able

to give them medicine to cure their ills or at least relieve their symptoms. Even though we have not as yet discovered any medicines that will cure coronary disease much can often be accomplished for the relief of symptoms. Moreover, medicinal treatment may be helpful in keeping patients alive following acute coronary occlusion and for the treatment of threatened or actual heart failure. These matters have been discussed at considerable length in textbooks and special articles and I propose to make only a few brief comments upon the practical application of certain forms of treatment.

It would be difficult to find a remedy more effective and less harmful than the nitrites for the relief of an attack of angina pectoris. Nevertheless many patients hesitate to use them except for a severe attack and consequently employ the medication only after the attack has reached its height. It is therefore well to instruct them in detail regarding the use of nitrites and make clear the fact that these remedies are not habit forming, that tolerance increases only slightly and does not persist, and that the drug is more effective if used early in a seizure. On the other hand, many patients who are given nitroglycerin for pains in the chest continue to use it believing it to be helpful when in fact it is not. Its effectiveness can be determined by ascertaining the time relation between placing a rapidly soluble tablet under the tongue and the beginning of relief. If this interval exceeds two or three minutes it is extremely unlikely that the nitroglycerin has anything to do with relief of distress, thus immediately bringing the diagnosis under question. There still seems to be some difference of opinion regarding the relative merits of amyl nitrite and nitroglycerin. The former acts more quickly but its effects are so transient that pain is more likely to recur in a few minutes. Although the dosage is more difficult to control, intelligent patients may become expert in its use, being able to inhale enough to relieve pain and still avoid unpleasant nitrite effects. Many patients prefer nitroglycerin because it can be used without attracting attention. Moreover if it is employed at the very beginning of an attack, it usually acts rapidly enough to prevent severe distress.

One of the questions often asked when a patient's treatment is under discussion is whether orally administered theophylline compounds or papaverine will prove useful. I know of no method by which one can predict their results in any given case. It seems unwise to continue using such remedies over long periods of time without trying to find out

whether they are really beneficial. One can usually obtain evidence on this point in reasonably intelligent patients by alternate periods of administration and withdrawal of the drug under consideration without making other changes in treatment at the same time. There seems little doubt that some patients are helped by such remedies and others not at all. Gastric irritation produced by theophylline or theobromine compounds, although apparently well known by everyone, may be frequently overlooked in practice because symptoms produced by the drug are attributed to the disease. One sometimes obtains greatest success in relieving symptoms merely by withdrawing such medicines.

The indications for the use of digitalis in the treatment of coronary disease are to some extent still a matter of controversy. Coronary disease unless life is terminated by one of the accidents that may occur during acute coronary occlusion such as ventricular fibrillation, rupture of an infarct or embolism, tends to progress slowly or rapidly toward left ventricular failure and its consequences. Experience seems to indicate that digitalis rarely benefits patients with angina pectoris and frequently aggravates this condition. It has some value in helping to prevent attacks of paroxysmal cardiac dyspnea. It is most useful in cases with chronic or established auricular fibrillation to help keep the ventricular rate under control. It is also useful in congestive failure. Digitalis is often administered to patients in advanced stages of coronary disease when rapid deterioration or sudden death are to be looked for. Nevertheless, the frequency of such occurrences at just about the time digitalis effects are obtained suggests that this drug is not without danger and if used even for the more chronic manifestations should be administered cautiously. Experimental studies seem to show that full digitalis dosage increases the mortality of animals with acute coronary obstruction. One may question whether it has any use in human acute coronary occlusion aside from the control of the ventricular rate in such abnormal mechanisms as auricular fibrillation, when there is reason to believe that the rapid rate is contributing to a dangerous grade of heart failure.

In the treatment of acute coronary occlusion the stakes are always death versus an unpredictable grade and duration of recovery. In an illness in which death may occur suddenly without forewarning or the patient who seems almost moribund may recover, one must be cautious in drawing conclusions as to the results of treatment. In deciding on a step in treatment one should give full weight to its dangers as well as

its possible advantages I have already referred to the possible danger of digitalis. Perhaps no one would deny the value of morphin or drugs with similar actions to relieve pain or restlessness but the last dose which relieves pain completely may produce depression of respiration and perhaps be responsible for the death of the patient. The intravenous injection of theophylline ethylenediamine is often followed promptly by a marked improvement of a profoundly depressed circulation thus averting what had seemed to be almost imminent death. On the other hand, too many patients die within a few minutes after such an injection even though it be given over a period of five to ten minutes, for the death to be always a coincidence. This danger I believe can be almost completely averted by administration of 0.5 gm. of theophylline ethylenediamine diluted with 200 cc. of salt or glucose solution by slow intravenous drip over a period of two hours. It can be repeated several times a day when necessary to sustain the circulation.

The value of oxygen, efficiently administered in high concentration in patients critically ill with acute coronary occlusion is beyond question. However, its use should not be postponed until the patient is critically ill. It often has great value in relieving pain, as can be demonstrated by stopping it temporarily, thus reducing the need for morphin. Moreover it may produce definite improvement in the circulation. Thus, there are reasons for believing that when given promptly it may prevent critical illness or death. The mode of administration is important. Nasal catheters and the masks in popular use are liable to annoy the patient and increase restlessness. A small transparent plastic hood covering only the head and upper chest, such as the one devised by Lambertsen and Godfrey,⁷ having the shape of an egg bisected longitudinally and attached to the ordinary air conditioning unit is highly efficient and much more satisfactory from the point of view of the patient and nurse as well as the physician, than any other apparatus I have used including large oxygen tents. Oxygen concentrations of 60 to 88 per cent can be maintained by an oxygen flow of 6 to 10 liters per minute. When the small hood is used, it must be kept under observation in desperately ill patients because of the undesirable concentration of carbon dioxide if the motor stops. It should therefore be removed when the nurse is to leave the room for any length of time.

SURGICAL PROCEDURES

The idea that some of the problems of circulatory disease can be

attacked by rendering ineffective certain functions of those parts of the nervous system which have to do with the heart and blood vessels although not new, is attracting more and more attention. Procedures designed to block pain impulses have a limited although worthy objective which is to make the patient more comfortable. Among such is the paravertebral alcohol injection procedure developed by Swetlow⁸ on the basis of Mandl's observation that angina pectoris can be relieved temporarily by the injection of procain into the same areas and J. C. White's⁹ operation of resection of sympathetic dorsal nerve root connections. That these procedures are capable of relieving anginal pains seems to have been established beyond question by competent observers. Personally I have had no experience with White's procedure and little with paravertebral alcohol injection because of the rarity in my experience of cases in which such measures seem necessary for the relief of anginal pain. After one has eliminated hiatus hernia, the varieties of spasm of the gastro-intestinal tract which may accompany gall bladder disease or nervous states, and the various somatic causes of pain in the distribution of the brachial plexus and intercostal nerves in patients who may or may not also have the anginal syndrome, there remain only a few in which nerve block for the relief of the anginal pain itself has seemed to me necessary or even desirable. However, I do not mean to imply that when severe pain, whatever its origin, cannot be relieved by simpler measures, relief should not be sought by nerve block.

It is entirely possible that the extensive sympathectomies now being employed for the treatment of hypertension may retard the development of coronary atherosclerosis in the patients operated on successfully by virtue of a lower blood pressure resulting from the operation. If this proves to be the case, the operation will prolong the lives of those who would otherwise have died as a result of coronary complications of their disease.

The success of sympathectomy in the treatment of peripheral vascular disease seems to depend in large measure on the extent to which vasospasm contributes to the deficiency of blood supply and its relief by operation. Moreover there is now some evidence to indicate that the development of collateral circulation is encouraged by a state of dilatation of vessels already in the neighborhood.¹⁰ If these statements apply to the heart as well as the legs, one of our objectives should be the development of an operation which will produce maximum vasodilatation

of the coronaries and another should be the development of procedures by which the grade of coronary vasospasm can be recognized so that the operation could be applied to suitable cases. By such means it is at least theoretically possible that some of the evil effects of coronary disease could be mitigated.

THE EVALUATION OF NEW FORMS OF TREATMENT

During the course of this discussion, I have repeatedly emphasized the gaps in our knowledge of coronary disease and the limitations of the modes of treatment at our disposal. For such reasons, medicine should be especially careful not to rest on its modest laurels in this field but be eager for new ideas and receptive to new proposals for treatment. However, we have the right to demand that they be based on the closely reasoned argument and precise recording that Sir Thomas Lewis¹ properly insists should characterize medical writings. The criteria upon which the value of a remedy should be based must include sufficient experience with it so that its possible disadvantages or dangers are recognized, accurate diagnosis so that one knows what he is treating and enough precisely recorded data so that the fallacy of post hoc, ergo propter hoc can be excluded. Without such requirements, we shall doubtless continue to have new forms of treatment recommended without adequate study, received by the uncritical with a wave of enthusiasm and then dropped when their lack of value is finally established. With insistence on scientific standards, we shall undoubtedly work our way forward, even though it be at times a slow and tedious process.

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USE OF CONCENTRATED HUMAN SERUM γ -GLOBULIN IN THE PREVENTION AND ATTENUATION OF MEASLES*^{1 2 3}

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I PLASMA FRACTIONATION

I INTRODUCTION

THE present world conflict has given a tremendous impetus to the practical application of knowledge concerning the blood and its many functional constituents. Whole blood has recently been flown from bleeding centers on our eastern seaboard to the European theatre of operations for use in the treatment of battle casualties within a few days of its collection. Blood plasma, its essential proteins preserved by methods for desiccation from the frozen state worked out in recent years, has been transported all over the world and stored till needed by the men of our armed forces.

Blood is a complex mixture of cells suspended in the plasma and performing many functions, not all of them known. The transfusion of blood has come to be used for the treatment of shock, anemia, infection, agranulocytosis, thrombocytopenic purpura, and the bleeding

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1 Both the clinical studies and the development of the products from blood collected by the American Red Cross have been carried out under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

2 The studies reported in this paper would not have been possible without the cooperation of a number of agencies and individuals. Most of the work in Boston in 1943 was carried on by Dr. Charles W. Ordman. Field tests of globulin preparations against measles in 1944 have been carried out with the assistance of the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, in Philadelphia and Baltimore under the direction of Drs. Joseph Stokes, Jr., Elizabeth P. Maris and Lt. S. S. Gellis, M.C., A.U.S. in New York City, through the Department of Health by Drs. Maurice Greenberg, Samuel Frant and David D. Rutstein in Washington, D.C., under Capt. L. R. Newhouser, M.C., U.S.N. and Dr. Lewis K. Sweet, in Durham, N.C., under Dr. W. C. Davison and in Boston and vicinity with the cooperation of the Massachusetts Department of Health, the Massachusetts Antitoxin and Vaccine Laboratory and the Health Officers of Arlington, Medford, Malden and Chelsea. We are indebted to the large number of physicians and hospital staff members in various cities who have provided most of the reports on which this study is based to Dr. William B. Berenberg and the house and resident staff of the Children's Hospital for their assistance in the control and distribution of globulin, and to Miss Virginia Poole, B.A., who has kept the records, tabulated the data and prepared the charts for this report.

3 This paper is No. 32 in the series 'Studies on the Plasma Proteins' from the Harvard Medical School, Boston, Massachusetts on products developed in the Department of Physical Chemistry from blood collected by the American Red Cross.

tendency of jaundice and hemophilia, although in only one of these instances, shock due to hemorrhage, are all of its constituents needed to repair the physiological defect. In many of these instances it should be more rational, more effective, and less wasteful to use only that component needed for the particular therapeutic purpose. Thus, the infusion of resuspended red blood cells, as reported by Taylor, Thalhimer and Cooksey¹ and by Cooksey and Horwitz,² is a logical use of the chief waste product of plasma production, and raises the hemoglobin level of the anemic patient rapidly without imposing on his circulation the necessity of disposing of the excess plasma. Unfortunately, methods for the separation or preservation of the more labile and less numerous granulocytes and platelets have not been developed.

In the case of plasma, we are dealing with a mixture of many types of protein molecules in a crystalloid solution closely corresponding in composition to the interstitial fluid of the body. The numerous protein constituents of plasma differ in their chemical properties, their source and fate within the body, and the functions which they perform.³ The isolation of these components in pure form and their chemical characterization has long been an aim of all those interested in human physiology. Military necessity has encouraged the accomplishment of this aim, and has thus opened up new horizons in the treatment and study of disease.

The plasma fractionation program, which originated in a desire to investigate the physiology of the individual plasma proteins, received a tremendous impetus from the need of the armed forces for a compact, safe and effective blood derivative.⁴ To meet this need, concentrated human serum albumin was developed and, under Navy contract, has been produced on a large scale from blood collected by the American Red Cross. The methods worked out by Cohn, Oncley, Strong, Hughes and Armstrong⁵ for the separation of pooled plasma into a series of fractions, from one of which albumin is prepared, have been devised in such a way as to make available as many as possible of the other functionally important plasma proteins. Thus there have been developed an increasing number of products of plasma fractionation which have useful clinical applications, while the development of others is still in progress.

2 THE PLASMA FRACTIONS

Table I lists the plasma fractions and their derivatives for which

TABLE I
BLOOD AND BLOOD DERIVATIVES

<i>Material</i>	<i>Fraction</i>	<i>Subfraction</i>	<i>Functional Component</i>	<i>Product</i>	<i>Use</i>
Whole blood			Cells, platelets, plasma		Hemorrhage
Resuspended red cells			Erythrocytes		Anemia
Plasma			Plasma Proteins		Burns, hypoprothrombinemia, hemophilia
Fractions of Pooled Human Plasma	I (Fibrinogen)		Fibrinogen (with thrombin)	Plastics Fibrin films Fibrin foam + thrombin	Dural substitutes Absorbable hemostatic agent Skin grafting
	II + III (α , β , γ -globs)	II (γ -globs)	Antibodies (60%)	γ -globin antibodies (Immune serum globulin)	Prophylaxis and therapy of infectious diseases
		III-1 (β + γ -globs)	Antibodies (40%) Isoagglutinins	Isoagglutinins	Blood grouping
		III-2 (β -globs)	Prothrombin Complement (C'1)	Thrombin	Hemostatic agent
	IV (α + β globs, Lipoproteins)		Hypertensinogen Complement (C'2) Thyrotropin Alkaline phosphatase		
	V (Albumins)		Albumin	Concentrated normal human serum albumin	Shock Edema Hypoproteinemia
	VI (Very little protein Chiefly salts)				

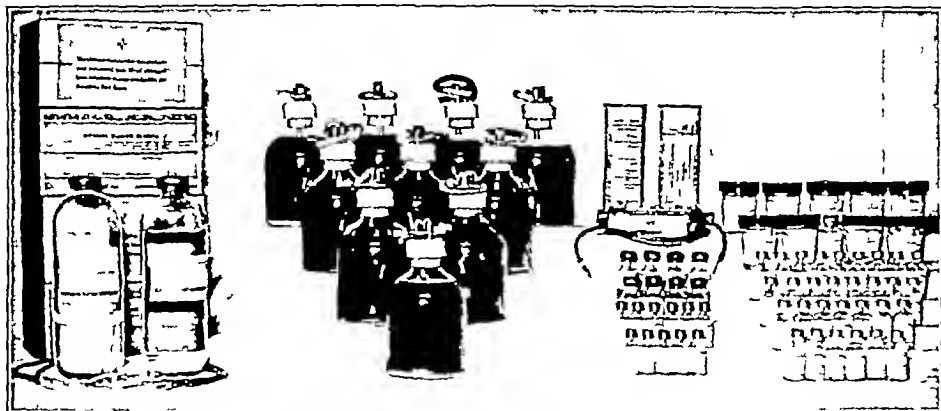


FIGURE 1

THE PRODUCTS WHICH MAY BE OBTAINED FROM 1110 BLEEDINGS IN THE CENTER

On the left are the five 500 cc dried plasma packages (2500 cc) obtained if all the plasma is used as such. On the right are shown the products of plasma fractionation now obtainable from this amount of blood. These comprise

1 Inner row (top) 3 packages of albumin (equivalent to 1500 cc of plasma in osmotic effect), (middle) 8 vials of isohemagglutinins (if blood of one group only is used), (bottom) 11 vials of globulin antibodies (55 cc.)

2 Outer row (top) 9 packages of fibrin foam, (bottom) 30 vials of thrombin

specific indications have been proved. The availability of these fractions has made possible progress along several lines. First, every donation of blood becomes far more useful if separated into its specific components and used in several different ways (See Fig. 1). Second, it becomes possible to achieve therapeutic results using concentrated and purified proteins for specific purposes, which would be difficult or impossible with whole plasma because of the amounts that would have to be given. Thus, in the treatment of hypoproteinemic edema, a large amount of osmotically active albumin can be administered in a small volume of fluid, without the salt which tends to exaggerate any form of edema. Third, using human plasma fractions as starting material, it is possible to develop entirely new products which can be used for purposes for which plasma is not suitable. Such products are fibrin foam with thrombin and fibrin film, now being used in various surgical procedures. Fourth, with purified proteins available as tools, it becomes possible to investigate many aspects of the physiology of the plasma proteins which are of fundamental importance to an understanding of health and disease.

3 THE PLASMA ALBUMINS

The plasma proteins have been divided by chemists into albumins and globulins. The albumins constitute a relatively homogeneous group of protein molecules which carry the highest net charge and are the most symmetrical, most stable and smallest of the plasma proteins.³ As a consequence of these chemical characteristics, the albumins exert 80 per cent of the colloid osmotic pressure of the plasma although they constitute less than 60 per cent of the total plasma proteins.⁶

Twenty-five per cent albumin solution, as dispensed in the standard Army and Navy package⁷ has approximately the viscosity of whole blood, can be kept for months without refrigeration and can be rapidly injected without reconstitution or preliminary cross matching. A single 100 cc package containing 25 grams is osmotically equivalent to 500 cc of citrated plasma but has only 1/6 the bulk or weight of the standard Army-Navy plasma package. The complete safety of albumin and its effectiveness in rapidly restoring a diminished blood volume and thus relieving the symptoms of surgical shock have been amply demonstrated.^{8,9,10} Once it becomes available to civilians, albumin should be ideal for the physician to carry in his bag or for hospitals to keep on the accident room shelf for the emergency treatment of patients in actual or impending shock.

However, albumin is more than a convenient and effective substitute for plasma, it is a therapeutic agent in its own right with application to certain situations where plasma is ineffective. It supplies a long-felt need in medicine and surgery for a protein solution which can be administered at any desired concentration and with any desired combination of electrolytes. Since albumin is the particular protein in which hypoproteinemic patients are almost always deficient, it is the logical one to administer in the relief of their symptoms. The work of Thorn and his associates¹¹ in demonstrating that a salt-poor albumin solution will produce diuresis in patients with the nephrotic syndrome is but one example of the many new therapeutic possibilities opened up by this development.

4 THE PLASMA GLOBULINS

The remainder of the plasma proteins are globulins, a group of proteins with diverse chemical characteristics performing many im-

portant functions in the body. These are divided on the basis of their electrophoretic behavior into α , β , γ -globulins and fibrinogen. Blood clotting requires the interaction of two globulins—thrombin, an enzyme which circulates in the form of its inactive precursor, prothrombin, and fibrinogen.¹² From these proteins have been developed fibrin film, used as a dural substitute, and fibrin foam with thrombin, used in surgery, neurosurgery and dentistry as an absorbable hemostatic agent.¹³⁻¹⁹ The isohemagglutinins are likewise globulins, and these have been concentrated from bloods of a single specific group for use in the typing of blood for transfusion purposes.²⁰⁻²¹ In addition, complement, certain hormones and enzymes circulate as, or in close association with, the plasma globulins, although their purification for clinical use has not yet been effected. Finally, we come to those globulins with which we are immediately concerned in this discussion, the antibodies.

Most antibodies are γ -globulins, that is, globulins which migrate most slowly in an electric field, due to their electrical asymmetry and low net charge. Although their net charge is low, the asymmetrical distribution of charges on the molecules of γ -globulin is such that their electric moment is high and their possibilities of interaction with other proteins or smaller molecules very great. The antibodies are quantitatively recovered from the plasma in Fraction II + III, and by the present methods for the further subfractionation of Fraction II & III, about 60 per cent of the antibody activity is recovered in Fraction II and 40 per cent in Fraction III—1. Clinical studies have been carried out with preparations of Fraction II which have been steadily improved until a purity of 95 per cent or better with respect to γ -globulin has been achieved.²² Methods for the recovery of the remaining 40 per cent of the antibodies in Fraction III—1 are now in process of development.

II γ -GLOBULIN ANTIBODIES LABORATORY STUDIES

When the plasma fractionation program was first undertaken, with the separation of the albumin fraction for transfusion purposes, Robinson pointed out the possible practical application of the globulin fraction to the control of infectious diseases. Accordingly, studies were initiated²³ which quickly revealed that the immune bodies present in the plasma pool were quantitatively recovered in Fraction II+III, a crude fraction containing some α —but chiefly β - and γ -globulins, whereas

the other Fractions, I, IV and V, contained a lower concentration of antibody than the original plasma Under the direction of Dr A R Dochez of the Committee on Medical Research, samples of Fraction II+III were sent to many investigators throughout the country, whose titrations revealed approximately 10-fold concentration over pooled normal human plasma of a large variety of antibodies These laboratory titrations were supplemented by the clinical tests of Stokes and his colleagues, who demonstrated that preparations of this fraction could be used for the prevention or modification of measles in exposed children

However, Fraction II+III contains a number of other important functional constituents besides the immune bodies to infectious agents and consequently further subfractionation was carried out, yielding three fractions III-2, composed chiefly of β -globulin and containing prothrombin, III-1, a mixture of β - and γ -globulins in which the isohemagglutinins are concentrated, and II, comprising chiefly γ -globulin, with marked antibody activity

Methods for the preparation of Fraction II have been gradually improved so that the γ -globulin content of this fraction, as estimated by electrophoretic analysis, has been increased from roughly 80 per cent to 98 per cent in recent preparations Enders²⁴ has carefully measured the concentrations of certain representative antibodies in each preparation of Fraction II for over a year, so that a statistically significant body of data has been accumulated on γ -globulin fractions derived from blood collected in the northeastern, midwestern and Pacific states This body of data shows considerable uniformity of antibody content despite the collection of blood at different seasons and in widely separated localities However, it was found last winter that the titer of antibodies to influenza A rose in preparations derived from blood collected after the cessation of an epidemic due to this virus This is an example of how the preservation of this fraction of pooled normal plasma as a stable dry powder might form an important record of the immune status of a population, thus providing the epidemiologist with a new tool, changes in antibody titers reflecting the sweep of epidemics through the group Since the pools from which these samples are derived represent from 2,000 to 6,000 donors, the antibody levels should be fairly representative of the immunity of the group rather than of a few exceptional individuals

TABLE II
TITERS OF REPRESENTATIVE ANTIBODIES

<i>Infection</i>	<i>Test</i>	<i>Fraction II Titer</i>	<i>Conc Factor over normal plasma</i>	<i>Conval- escent plasma titer</i>	<i>Ratio Titer II Conv plasma</i>
Typhoid	H Agglut	94	20	2000	1/20
	O Agglut.	10	2	900	1/90
Influenza A	Comp Fixation	280	20	360	8/10
	Hirst Test	308	10	500	6/10
	Mouse Prot	130	23	210	2/3
Mumps	Comp Fixation	98	20	250-1300	1/13-1/4
Diphtheria	Antitoxin (units/cc)	26	25	(13)	(20)
Scarlet Fever	Antitoxin (units/cc.)	40	22	5-15	2-5
B-Streptococcus	Antistreptolysin (units/cc.)	2500	25	500	5

The antibody titrations carried out under Enders' direction have been used to control the potency of the serum γ -globulin preparations as they have come from the Harvard Pilot Plant and from commercial laboratories operating under contract with the Navy or the American Red Cross. Although considerable variations may occur in these titrations due to inherent difficulties with the tests, all the antibodies followed have been found concentrated from 15 to 30 times in Fraction II. From the chemical standpoint the concentration with respect to γ -globulin is approximately 25-fold. These facts, combined with the association of antibody activity in most hyperimmune animal sera with the γ -globulin fraction and the finding that the antibody titers have not fallen as all but traces of β -globulin have been removed from recent preparations, suggest that most antibodies of normal human blood are γ -globulins.

Although there is a parallel concentration of γ -globulin and antibody in Fraction II, only about 60 per cent of the total antibody activity of Fraction II+III can be accounted for in it. The remaining antibody activity is found in Fraction III-1, which contains both β - and γ -globulins, and studies are now in progress which should make it

possible to recover this moiety for clinical use. One very interesting finding is the behavior of the two typhoid agglutinins. The H or flagellar antigen of the typhoid bacillus is a protein and its agglutinin, like the majority of other antibodies, is concentrated in Fraction II. On the other hand, the O antigen contains a polysaccharide and its agglutinin is concentrated to a marked extent in III-1, as are the iso-hemagglutinins whose homologous antigens are not protein, but polysaccharide in nature.

Table II indicates the levels of those antibodies which have been carefully followed a sufficient number of times to give an accurate idea of the concentrations to be expected. It will be noted that the concentration factor over normal plasma corresponds closely to the concentration factor for γ -globulin in all but two instances, the typhoid O agglutinin, discussed above, and the Hirst test, in which, for technical reasons, false low readings are obtained. The ratio of the titer of Fraction II to reported values for convalescent plasma gives some idea of those diseases, in which, other factors being equal, γ -globulin might be expected to have some clinical effect. It may readily be seen that γ -globulin approaches the values for convalescent serum in the case of influenza A, it falls far short in typhoid and mumps, while in scarlet fever, and probably diphtheria, it exceeds them.

The process of concentration of the antibody activity of normal human plasma into a single fraction is not only important for the preparation of an effective prophylactic and therapeutic agent, but also for the preservation of this activity for the future. In the process of preparing normal human serum albumin for the armed forces, the plasma from many donors has been subjected to fractionation. This has made available a large amount of human antibody. It has been found that when this is kept properly as dry powder or as the final solution, it is stable for long periods of time. This stability is increased by the use of 0.3 molar (isotonic) glycine as diluent in place of sodium chloride, a change which has been incorporated in the most recent preparations of γ -globulin antibodies. The excellent keeping qualities of human antibodies when concentrated and refined is of great practical importance, since it makes feasible the plan, inaugurated by the American Red Cross with the cooperation of the Navy, for the distribution of γ -globulin in excess of the needs of the armed forces, to the people of the United States through public health agencies.²⁵

III CLINICAL USE OF γ -GLOBULIN ANTIBODIES

1 GENERAL

The use of human blood, plasma, or serum to transfer passive immunity against a number of infections is an established clinical procedure, although the evidence for its effectiveness has not been clear in every case. In some instances normal serum has been used, more frequently convalescent serum, and in the case of pertussis, hyperimmune serum (i.e., the serum of donors already immune whose antibody levels have been further increased by stimulating doses of vaccine). The use of human blood as a source of antibody has the great advantage of freeing the recipient from the dangers and discomforts of the serum disease which so frequently followed the injection of unconcentrated animal sera in earlier days and which still is occasionally seen after administration of the refined and concentrated sera of the present. The difficulty with human antibody preparations in the past has been that their potency has been low, their standardization usually has not been carried out except in the patient, and convalescent sera have often been hard to obtain. Furthermore, the recent evidence incriminating human blood,²⁶ plasma²⁷ and serum²⁸ in the transmission of an agent causing jaundice from donor to recipient has cast some doubt on the relative safety of human as compared to animal serum. The use of γ -globulin obviates many of these objections to the use of human antibody in the form of serum or plasma.

In discussing the use of γ -globulin we shall refer to the injection of antibody before symptoms of disease appear as *prophylaxis*, whether the attempt is to prevent or modify the symptoms, and to the injection of antibody after symptoms have occurred as *treatment*. Two groups of factors will influence the results of passive immunization for either of these purposes. First come the quantitative factors: (a) *the antibody level established in the patient*, which is influenced by the concentration of antibody in the immunizing agent, the size of the dose, the size of the patient, the speed of absorption, and the rate of destruction of antibody in the body, (b) *the antibody level necessary for neutralization* of the toxin, bacterium or virus producing the disease, and (c) *the time of administration of the antibody* in relation to exposure and the length of the incubation period. Second, come the qualitative factors relating to the nature of the infectious agent and the pathogenesis of

the disease. These include its portal of entry, sites of multiplication, incubation period, route of spread, and the stage at which the disease can be recognized. Unfortunately, in the case of measles, the disease for which the efficacy of γ -globulin as a prophylactic agent has been unquestionably proved, quantitative data can only be obtained in humans exposed to the disease, since no laboratory test for antibody to this virus has yet been found.

2 THE USE OF γ -GLOBULIN IN THE PROPHYLAXIS AND TREATMENT OF SPECIFIC INFECTIONS

A *Measles*

(a) *Historical background* Measles is a disease for which human blood provides the only known source of antibody. Attempts to produce a satisfactory vaccine for human immunization have not met with success, and therefore it still remains one of those diseases which everyone must have sooner or later. Unlike many virus diseases, the process of acquiring immunity to measles is almost invariably associated with the development of the clinical picture of the disease, although considerable variation in its severity may occur. Immunity to measles is present in the first few months of life provided the mother is immune to this disease. In the transition from the immunity of infancy to the extreme susceptibility of early childhood, there is a period when measles may assume rather mild and atypical forms, presumably because the child has the very low levels of antibody required to attenuate the effect of the virus.

The use of human blood or its derivatives for the prophylaxis of measles has become a standard pediatric procedure. Two alternatives are open to the physician: first, to prevent the disease completely, or second, to attenuate the disease to such an extent that it becomes a relatively minor infection. It is desirable to prevent all symptoms of the disease in sick or debilitated children, in infants between 6 months and 3 years, and in children who must travel or who are on hospital wards where they will expose other sick children. In producing attenuation, the physician is really performing serovaccination, using passive immunization in such a way that the child acquires an active immunity. This is a satisfactory method of active immunization except for the fact that it can only be used when the patient is known to have been exposed to the disease. Two fundamental premises underlie the pro-

cedure (1) that a mild attack of measles is less dangerous than a severe attack, and (2) that a mild attack of measles produces a lasting immunity. We believe that results achieved with γ -globulin and convalescent serum justify the first premise. To our knowledge, no satisfactory large scale follow-up studies have ever been made which would yield convincing evidence upon the second. However, it is rational to believe that modified measles confers on most individuals a relatively permanent immunity, since spontaneous mild cases of the disease appear to confer protection for life, and there is a general impression that most children who have modified measles do not develop subsequent attacks.

Various sources of human measles antibody have been employed in the past. Whole blood has often been used inadvertently in hospitals. We have recently seen a very mild case of measles occurring seven days after a transfusion in a patient on our own wards. Convalescent serum is, unfortunately, somewhat difficult to obtain in adequate amounts and convalescent serum, or particularly normal adult serum, must be given in rather large doses to be effective. Consequently the discovery by McKhann and his associates²⁹ that it was possible to extract from human placentas antibody against most of the infections to which the average adult is immune provided a readily available preparation for the prevention and modification of measles which has found widespread use. It seems probable that the placenta itself does not manufacture antibodies but merely allows them to pass from the maternal to the fetal circulation and therefore is a good source of measles antibody because it contains a large amount of blood. The chief difficulty with placental extracts (marketed under the name of Immune Globulin) has been the relatively high incidence of reactions following their use. Their potency in general has not been sufficient to afford complete protection in most cases, although they have been fairly satisfactory for attenuation of measles. These disadvantages have been recently demonstrated in a comparison of γ -globulin with placental extract, made in New York City by Greenberg, Frant and Rutstein³⁰.

(b) *Use of γ -globulin in prophylaxis of measles* (1) *Results* Stokes, Maris and Gellis³¹ first demonstrated the effectiveness of γ -globulin in the prophylaxis of measles, and their result were confirmed by Ordman, Jennings and Janeway.³² Subsequently, with the cooperation of a large number of physicians in various parts of the country it has been possible to amass a large number of cases for statistical study. These have proved

TABLE III

COMPARISON OF RESULTS OF PASSIVE IMMUNIZATION AGAINST
MEASLES WITH VARIOUS AGENTS (UNSELECTED CASES)

<i>Immunizing Agent</i>	<i>Total # Cases</i>	<i>% No Measles</i>	<i>% Mild Measles</i>	<i>% Average Measles</i>
Convalescent Serum ¹	1627	75	17	8
Normal Adult Serum ¹	584	56	24	20
Placental Extract ¹	2740	64	31	5
γ -Globulin Antibodies	2738	73	24	3

1 From McKhann (29)

beyond question that γ -globulin provides the physician with the most effective agent for the prevention and modification of measles that is available. The data can be presented best in a series of tables. Table III gives comparative data for various preparations which have been used for this purpose in the past and for γ -globulin, as judged from the over-all results in a large series of unselected cases. Since these figures include all ages and all degrees of exposure, their significance is open to some question. In Table IV will be found the figures for γ -globulin and convalescent serum in comparable groups of children under 12 years of age, intimately exposed within the home. The expected attack rates for the groups are given, as determined by the excellent painstaking studies of Stillerman and Thalheimer³² in New York City for several years and by Ordman³² in 1943 in Boston. It can be seen that the results with convalescent serum are as good as with γ -globulin, but the doses necessary are larger.³⁴

2 *Dosage* A physician using an agent such as γ -globulin would like to feel sure that he could achieve complete protection for his patient or satisfactory modification of the disease at will. Unfortunately, he is dealing with a biological system in which the two biggest variables, the susceptibility of the patient and the virulence of the virus, are beyond his control, so he must be content with some failures. In order to obtain complete protection, it is axiomatic that he should give as big a dose as possible as soon after exposure as possible. To modify the disease, he may either delay his injection until it is too late in the incubation period to prevent the disease or he may use a smaller dose

TABLE IV

RESULTS OF PASSIVE IMMUNIZATION AGAINST MEASLES WITH
 γ -GLOBULIN ANTIBODIES AND CONVALESCENT SERUM

(Selected Cases, Home Exposure, Age Under 12)

	<i>Total # Cases</i>	<i>% No Measles</i>	<i>% Mild Measles</i>	<i>% Average Measles</i>
Attack Rate ¹	54	20	4	76
Attack Rate (0-14 yrs) ²	266	25	75	
γ -Globulin Antibodies (6 mos—12 yrs) (Dose 0.5-5 cc.)	1570	65	32	3
Convalescent Serum (6 mos—15 yrs) (Dose 5-20 cc.) ³	502	50	49*	1

1 Ordman (32)

2 Stillerman and Thalhimer (33)

3 Stillerman, Marks and Thalhimer (34)

* 27 per cent so greatly modified that without close observation 77 per cent might have been classed as having no measles 4 per cent slightly modified, cases which we probably should have classified as average measles

of globulin Which will give the most reliable results? An analysis of our data for the selected group of cases indicates that the physician has a greater chance of producing attenuation or complete suppression of measles, according to his desire, by varying the dose of globulin than by varying the time of its administration This is clearly shown by the figures in Tables V and VI Ordinarily measles in the primary case is not recognized until the third or fourth day after onset, when rash or Koplik's spots appear If, at this point, the physician administers a suitable dose of globulin, he has about a 3 out of 4 chance of accomplishing his aim Suitable doses appear to be as follows

For protection (first 6 days after exposure) 0.08-0.1 cc/lb

For modification (first 8 days) 0.02-0.025 cc/lb

(When administered later in the incubation period, the dose should be increased)

Greenberg, Frant and Rutstein³⁰ in a study of γ -globulin suggested by Dr William Thalhimer and carried out by the Health Department of New York City have shown that, using a standard 2 cc dose of globulin

TABLE V

RELATION OF TIME OF INJECTION OF γ -GLOBULIN TO RESULTS
(1024 Cases, all doses)

<i>Time after exposure</i>	<i>% No Measles</i>	<i>% Mild Measles</i>	<i>% Average Measles</i>
0—2 days	64	35.2	0.8
3—5 days	66.8	32.2	1
6—8 days	51.6	42.7	5.7

TABLE VI

RELATION OF DOSE OF γ -GLOBULIN TO RESULTS
(1024 Cases, first 8 days)

<i>Dose (cc/lb)</i>	<i>% No Measles</i>	<i>% Mild Measles</i>	<i>% Average Measles</i>
0.1 — 0.375	83	63.1	3.9
0.375—0.75	55.2	40.6	4.2
0.75 — 2	83.7	15.5	0.8

and a standard time of injection, the degree of protection varies inversely with the age of the patient. This confirms the validity of calculating dosage on a weight basis.

3 *Duration of immunity* Undoubtedly, the duration of immunity will bear a direct relation to the size of the dose given and to the condition of the patient. For example, a patient with nephrosis might lose the antibody rapidly in the urine, or a patient with high fever might be expected to destroy it more rapidly than normal. In our experience a protective dose gives complete protection for 2-3 weeks in a normal child and should be repeated after 3 weeks if complete protection is still desired in the face of a new exposure.

4 *Safety* The globulin is administered intramuscularly, in the buttocks if a fairly large dose is given. In ordinary doses with a good needle, the injection is practically painless. The incidence of reactions in a large series of cases has been exceedingly low, and most of these have been very mild local reactions (Table VII). Care should be taken

TABLE VII
REACTIONS ON INJECTION OF γ -GLOBULIN

<i>Type of Reaction</i>	<i>Number</i>	<i>Per Cent</i>
Local	17	0.6
Febrile	12	0.4
General*	6	0.2

2738 injections 35 reactions, 1.2%

* Headache 1, Dizziness 1, Loose stools for 48 hrs after injection 2, Orbital edema 1

to check that the needle does not enter the vein, since the standard preparation is not suitable for intravenous use

One of the important clinical syndromes which has recently been recognized is that of homologous serum or inoculation jaundice³⁵. This disease, which may or may not be caused by a virus identical with that of epidemic hepatitis (catarrhal jaundice), occurs after an incubation period of 3 to 6 months following the injection of occasional lots of human serum or plasma derived from small pools. Presumably the infective agent circulates for some time in the blood of patients who subsequently come down with typical symptoms of epidemic hepatitis. It has sufficient resistance to withstand inactivation at 56° C for an hour, the process of desiccation from the frozen state, and fairly long periods of storage in the ice box. We have naturally been very much concerned about the possibility of transmitting this virus by the injection of γ -globulin. The statistical chances of this seemed somewhat greater than with convalescent serum because the pools of plasma were derived from several thousand donors. For this reason we have made follow-up studies from 3 to 6 months after injection in as many instances as possible. Out of 294 individuals so followed after the season of 1942-43, only one case of jaundice was observed, this occurred 3 months after injection and probably was pure coincidence since 73 other children who received this preparation did not develop jaundice. During the past season, 1943-44, we were able to follow up 869 individuals, none of whom has developed jaundice.

5 *Modified measles* The disease which results when an attenuating

TABLE VIII

COMPLICATIONS OF MEASLES IN CHILDREN UNDER 12 RECEIVING
γ-GLOBULIN

(1570 cases, 497 cases of mild measles, 54 cases of average measles)

<i>Age</i>	<i>Dose cc /lb</i>	<i>Days from exposure to injection</i>	<i>Result</i>	<i>Complications</i>
2 yrs	02	9	Severe measles	Staphylococcus aureus pneumonia and empyema with recovery
11 mos	025	6	Average measles	Mild encephalitis with recovery
2 yrs *	025	—	Average measles	Otitis media, simple
4½ yrs	017	6	Mild measles	Otitis media, simple
4 yrs	028	5	Mild measles	Otitis media, simple

* Child had reaction with chills, fever and edema of eyelids day after injection of globulin

3 complications in 54 cases of average measles incidence = 5.5%
2 complications in 497 cases of mild measles incidence = 0.4%

dose of globulin is given at the proper time after exposure may vary from a barely recognizable illness lasting a day, with very slight fever and a faint sparse rash, to one which is but little milder than the ordinary case of measles. In general, the malaise, prostration, and catarrhal symptoms are little in evidence, and fever and rash are the only signs of infection, but any combination of symptoms may occur. The incubation period is somewhat prolonged at times, perhaps because the disease is not recognized until the rash appears, but the duration of symptoms is rarely over two or three days. A number of patients have been observed in whom mild catarrhal symptoms without rash occurred at the proper time after exposure and were presumably due to the disease. Other patients who have received globulin have developed a few pinkish macules, particularly over the upper trunk, from 12 to 18 days after exposure, as the only sign of infection.

Complications appear to be infrequent with modified measles. Stillerman, Marks and Thalheimer³⁴ observed complications in 10 per cent of 502 children given convalescent serum for measles prophylaxis. In a boys' school where globulin was administered to half of the remaining

TABLE IX

USE OF γ -GLOBULIN TO CONTROL OUTBREAKS OF MEASLES
ON PEDIATRIC WARDS

	<i>No Outbreaks</i>	<i>No Children</i>	<i>Not Followed</i>	<i>No Measles</i>	<i>Mild Measles</i>	<i>Average Measles</i>
Number	39	395	95	286	13	1
Per cent	—	—	—	95.3	4.3	0.4

susceptible boys during a severe measles epidemic, there were five cases of otitis media and two cases of sinusitis in a group of fifteen uninoculated boys with measles and only one mild case of otitis media in an equal number of immunized boys who contracted the disease³² In the series of cases reported to us by various physicians the incidence of complications has been approximately ten times as high in the small group among whom globulin failed to modify the disease as in the large group among whom the disease was attenuated (Table VIII)

6 *Control of measles in pediatric wards* Outbreaks of contagious disease are a source of frequent difficulty in the administration of pediatric wards and institutions for children. The availability, safety and reliability of γ -globulin makes it particularly valuable for the control of such outbreaks. γ -globulin has been administered to children exposed in 39 outbreaks of measles in hospital wards. Table IX gives the results. These have been so good that when a case of measles occurs on our wards, we now only isolate the primary case and give a protective dose to the remaining susceptible children. Thereafter, any non-immune children admitted to the ward in the next 3 weeks should probably be immunized, but in practice we have immunized the newcomers only if mild measles develops in any of the original group.

c *γ -globulin in the treatment of measles* Measles differs from many virus diseases in that its course can be influenced by antibody even after clinical symptoms have begun. Stokes, Maris and Gellis³¹ were able to modify the course of the disease in a number of instances if they administered large doses of γ -globulin (15-30 cc) after the onset of the catarrhal stage but before the rash appeared. Stokes³⁰ has pointed out that, in the absence of chemotherapeutic agents for virus diseases,

the possibility of treating many of them with antibody still exists, provided the disease can be recognized sufficiently early

B OTHER DISEASES

There are a number of other infectious diseases for which it is conceivable that γ -globulin might provide a possible means of prophylaxis or therapy. *Chicken pox* is, if anything, a greater nuisance than measles on pediatric wards, but it is doubtful from the incomplete evidence yet available whether γ -globulin provides an answer to this problem. Although a fair titer of *mumps* complement-fixing antibody is present, Stokes and Enders³⁷ showed that in 10 cc doses, γ -globulin would not protect susceptible children against this infection. As yet, no clinical studies of the utilization of the antibody against *influenza A* have been undertaken.

The fact that γ -globulin contains scarlatinal antitoxin in 2-5 times the concentration of most pools of scarlet fever convalescent serum has led to clinical trials of its effectiveness in the treatment of *scarlet fever*. These studies are incomplete as yet, but there is reason to believe that concentrated γ -globulin may prove of value in both the therapy and prevention of scarlet fever.

IV SUMMARY

- 1 Concentrated human serum γ -globulin derived from blood collected by the American Red Cross contains a 25-fold concentration of most of the antibodies present in normal adult serum. This makes it possible to give the equivalent of 125 cc of pooled adult serum in a single intramuscular injection of 5 cc.

- 2 This material is now being distributed by the American Red Cross, through Public Health agencies, for the prevention and modification of measles, a purpose for which it has been proved particularly effective and safe.

- 3 When administered in the first six days after exposure to measles, a dose of 0.08-0.1 cc per pound will give protection to roughly three out of four individuals, with mild measles in the fourth, while a dose of one-quarter this much, or 0.02-0.025 cc per pound will result in an attack of mild measles in most cases.

- 4 In a large series of cases, very few reactions to intramuscular injection of the globulin have been observed, and these have been mild.

and chiefly local

5 The complication rate in modified measles appears to be definitely lower than in the typical disease

6 Studies are in progress to discover other clinical uses for this convenient form of concentrated human antibody

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BULLETIN OF
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MAY 1945

SOME PSYCHIATRIC ASPECTS
OF NERVOUS SYSTEM INJURIES *

WALTER O KLINGMAN, Lt Colonel, MC, AUS

THE variety of problems produced by nervous system injuries has become increasingly important with the progress of the war. This has called forth a careful appraisal, assessment and formulation of adequate treatment of the peculiar interrelating special surgical, neurological and psychiatric problems involved. This applies particularly to a large group of cases with a disability picture that is labeled "psycho-neurosis" or belong to the group labeled "post concussion neurosis" or "compensation neurosis."

The varieties of post-traumatic reactions in terms of relationship between the severity and nature of the injury itself and the somatic and personality responses are often difficult to differentiate, to treat medically, and to rehabilitate socially and economically. It is hoped that the accumulated experiences of many workers now confronted with these problems will give us a more comprehensive knowledge and more efficient therapy with which to meet these situations in both military and civilian cases. Because of the difficulties encountered in differentiation of the traumatic and post-traumatic reactions, classifications of the psychiatric disturbances have not been too satisfactory. The military or war injuries introduce complications which differ in

* Read November 14, 1944 at the Combined Meeting of The New York Neurological Society and the Section of Neurology and Psychiatry.

some respects from nervous system injuries sustained in civilian life. The combination of natural anxieties and tendency to worry or be concerned with prolonged war stress, sense of grievance, constitutional predisposition, malingering or the simultaneous development of a psychoneurosis under circumstances of exhaustion and fatigue, make for added confusion, particularly when there is also structural nervous system change.

In considering the symptoms of acute mental disturbance as a result of general cerebral injury, the most constant results of such injury from the psychiatric standpoint are the disturbances of consciousness. These range from states of transient interference in mild injuries to profound and prolonged states of coma in the most severe cases. Various grades of unconsciousness range between these extremes and for varying lengths of time.

The return from stupor or coma to normal consciousness is usually through a series of stages: coma, stupor, excitement or delirium, combativeness, aggressiveness, confusion and automatism. After full consciousness returns, the patient often is fully oriented but has a period of amnesia, frequently of a retrograde character or a mental haziness which dates from several minutes to hours prior to the injury and extends through until the final return to normal consciousness. This period or gap in the consciousness usually remains as a permanent defect. The return from the state of coma or stupor to consciousness may be associated from minutes, hours, days or weeks with states of semi-coma, confusion, motor activity and conversational ability but throughout the period there may be complete disorientation and inability to maintain sustained thought or expression. This state may be difficult to differentiate from other states of complete dissociation, particularly in the combat area, especially when there is no external evidence of a head injury.

In mild injuries momentary states of confusion or being dazed may be followed by an automatism like that described in cases of epilepsy or following electric shock therapy in which the individual may continue his activities either in a normal or abnormal manner and then may recall no part of them. This also, in the combat area, may lead to confusion, make for unintelligent behavior and totally incomprehensible actions. In injuries of this grade, then, an amnesia and automatism are the striking features.

In other types of mild injury without initial loss of consciousness there may be a form of delayed collapse after minutes or hours, some confusion of an in and out character, momentary blacking out, with or without automatism, supposedly due to an instability of the cerebral circulation consequent upon injury to its vasomotor apparatus, probably the result of damage to the brain stem

In the severe brain injuries the individual is usually profoundly comatose and shocked. If he lives, coma eventually becomes less deep and the series of events already described begins and much depends not only on the concussion but on the individual's personality. With higher psychical functions temporarily suspended, the content of lower levels stands revealed, whether as a result of edema or from the effects of concussion itself. In these severe cases complete recovery does not always follow and signs of local damage are likely to be found and recovery may never reach the completely normal state. Specific defect disorders, emotional and cognitive changes may appear in the post-confusional state.

Conscious activity comprises many different functions which must all be present before the behavior can be said to be normal. Any of these functions can be eliminated selectively by various types of brain lesions. Speech may be impaired by lesions in the temporoparietal area of the cortex. Lesions of the occipito-parietal area may give rise to other special defects. The same rule of breakdown and recovery after cerebral lesions applies to the other higher cerebral functions—memory, orientation, perception and imagination, and maintenance of emotional attitudes and stable behavior patterns. Elimination of any of these functions resolves itself into a restriction of the background specific to that function. It is on the proper activity of this background that the function itself depends.

Apart from residual symptoms due to such local structural damage as has been mentioned, in some cases symptoms indicative of more general disturbance of cerebral function may persist for varying lengths after cerebral injury and may even be permanent. This is especially true in elderly and arteriosclerotic subjects, where some degree of mental defect is more apt to ensue. These defects express themselves chiefly as defects of memory and of judgment with impaired emotional control, easy fatigue of both attention and of physical effort. These symptoms frequently do not stand in any close relationship to the clinical

severity of the original injury

As a rule most head injuries tend to recover completely and one infers that no structural damage has been sustained by the brain. In the others, however, it is difficult from then on to correlate persisting symptoms where recovery stops short of complete, as lesions may be present in the total absence of specific signs and symptoms. With the resources now available to us, disorders of cerebral function are more readily associated with discoverable and demonstrable lesions. Much recent outstanding work has been done towards assessing the severity of brain damage and is bringing us closer to more nearly accurate appraisals.

By far the commonest residual syndrome is that of headache, dizziness and emotional instability. This may persist for many months or for many years, is more apt to be long lasting in middle aged and elderly persons and often in patients whose injury is compensable or is carried on as a full expression of a psychoneurosis, sometimes of other origin than the cerebral trauma itself. Lesions in specific parts of the brain may facilitate neurotic reactions of the total personality and the organic consequences of head injuries may become the nucleus around which neurotic attitudes crystallize. The organic nucleus may be transformed, therefore, into that of the neurotic.

This suggests that in the syndrome or in the origin of the psychoneurosis, there is an interplay of physical and psychological factors. Unfortunately, the clinical criteria by which we might hope to distinguish psychogenic from physical elements in this symptomatology are by no means that distinct. At this time it is not considered possible to list or classify by any particular symptoms or criteria, for any symptom may have either psychoneurotic or organic basis, be due to diffuse degenerative change, focal or transient damage or be the expression of a latent psychoneurosis by a generalized physical effect.

Up to this point the psychiatric management of cerebral injuries should be confined to the needs of the immediate post-traumatic state. Very definite improvement in the procedures of management of head injuries in this war has been made soon after stabilization or clear consciousness is regained. Graduated programs of activity are frequently started within 24 to 72 hours after regaining consciousness with return to light duty in two weeks and full duty in six weeks time. One of the outstanding features in this early handling of these cases is the attempt

at complete divorcement from the idea that the injury is serious because it involves the head, that caution must be exercised from over-doing mentally and that such things as dizziness, headaches and nervous symptoms are to be expected. It also helps to eliminate the period of incubation in which the patient is meditating upon the suffering and derangement of his life caused by an accident for which, in most instances, he knows some one else may possibly be made legally responsible. The element of suggestibility by thoughtless reminders on the part of doctors and nurses can be potent factors. Furthermore, the Army hospital is not, as a rule, convenient for frequent visiting or any visiting by well meaning relatives, friends and claim agents who may be so helpful in building that post-traumatic crippled personality of civilian life. On the other hand, in an inaccessible theatre of military operations, treating a patient with head injury who may be emotionally unstable is not prognostically the same as the individual elsewhere, so that the element of secondary gain may be a potent factor in the production of a neurosis in the military theatre of operations. However, by and large, this new important step of immediate post-traumatic management and elimination of the incubation period has gained many converts among the neurosurgeons and neuropsychiatrists in this war.

The incorporation of convalescent and rehabilitation programs, the like of which is difficult to emulate in any civilian hospital, must be credited with much of the reversal of opinion regarding early post-trauma management of cerebral injuries when, not so long ago, prolonged bed rest, reduced physical and mental activity, restraint from duties for many months to a year was not an unusual prescription.

In this early activity phase there is introduced the psychological help calculated to strengthen the ego. Persuasion, strong suggestion, re-identification with the group, and stimulation of the ego-ideal result in an earlier return to active duty status before the stage of actual neurosis formation may be reached. Convincing reassurance, firmness in the pressure to return to duty and strong suggestion is most conducive to avoid binding anxiety to a symptom. Despite this, however, the physiological consequences of the trauma in many cases affect the function and structure of the brain to the extent that they offer material for the neurosis. The trauma brings about psychological change or activates latent or active neurosis of considerable severity. Fear of future ill health and unemployment are frequent natural factors.

When the elements of neurosis begin to dominate the picture the symptoms begin to assume bizarre qualities and to be complained of as being very disabling. Headaches not only become more continuous and fantastic but many other complaints are added. The emotional attitudes change and it is very difficult to explain the attitude perversions on the basis of structural damage to the brain. When these symptoms and changes become apparent, the time then has arrived to evaluate the symptoms and assess the role of psychobiological factors in the symptom complex.

At this point where the elements of a neurosis begin to dominate the picture we again find that there has been definite advancement in psychiatric management. Cases, particularly with anxiety and hysterical features, comprise a high percentage of these reactions, but almost any clinical expression of the psychoneurosis may become manifest. Our first duty is to strive for some appraisal of the physio-psychological aspects of the nervous system injury and attempt to estimate separately the organic residua and psychoneurotic symptoms. Just as in the medical and surgical treatment of nervous system injuries, each case must be studied and treated according to its particular merits. No injury is such a clinical entity for which a cut and dried line of treatment can be prescribed. This is also true of persistent after-effects.

In their order and when necessary, the following are indicated in the clinical evaluation at this point: (1) Painstaking neurological examination (2) Evaluation of emotional factors and thorough attempt at a sound, rational understanding of possible conflict between the unconscious sources of anxiety and the ego forces together with an understanding of the symptoms produced by psychological defenses, regressions and collapse (3) Psychological testing by specialized techniques, such as the Rorschach, Shipley-Hartford and others (4) Electroencephalography (5) Pneumoencephalography.

Some discussion of these evaluations warrant attention, particularly the evaluation of the emotional factors and methods for combating them. Again, we have profited by the experience of this war in the form of brief psychotherapy instituted in some theatres soon after the appearance of the traumatic neurotic expression, whether it follows injuries to the cerebrum or not. Narcoanalysis, narcosis therapy or narco-synthesis cannot be called exactly new since they have been used in civilian practice for the last ten years or so. Their free use, however,

has been necessitated and catapulted into the foreground by the urgent demands for quick brief therapy in the armed forces. This stands quite in contrast to the last war where rest, sedation and persuasion were chiefly used.

Actually, the application of this technique in prevention and treatment of neurosis following nervous system injuries has added to the understanding of the dynamic conflict between the unconscious sources of anxiety and the ego forces and to the evolvement of short term techniques derived from psychoanalytic principles. In this, time has been gained in that the period necessary to work through resistances in an effort to bring repressed emotions to consciousness has been eliminated. Likewise, uncovered anxieties can be tolerated without lengthy preliminary strengthening of the ego.

Conditions of war bring new factors to play upon the soldier's ego that are distinctly different from the conditions that prevail in civilian life as a result of accidents. The civilian traumatic neurosis occurs usually as a result of a single violent stimulus. The soldier, however, rarely develops his traumatic neurosis as the result of a single experience but as a result of accumulated stimuli, difficult physical conditions, intolerable environmental conditions, protracted separation from supporting and friendly human relationships and of sudden disruption of close personal ties with dead, wounded or injured comrades. The injury here is often the stimulus for a new and serious conflict with the ego ideal, inducing and provoking thereby the psychoneurotic expressions. Narcoanalysis followed by psychotherapy as the patient recovers from the narcosis results often in dramatic release of the unconscious psychological tensions, strengthens the ego forces and decreases the severity of the super-ego pressure. This has resulted in quick return to duty or combat or, at least, return to limited military service status, and in others it has offered the first steps to return to civilian life as useful members of society. This is particularly true of the cases with old latent anxieties and resentments dating back to civilian or early life periods.

Reactions of a depressed nature can be treated with convulsive shock therapy but must be carefully selected. This is another aid available in this war that was not at hand in World War I.

In the cases where it is difficult to distinguish the degree of physiological-psychological damage as a result of trauma, careful neurological examination must be relied upon and, just as the internist may turn to

the laboratory for a final decision, the neuropsychiatrist calls upon laboratory procedures for help. Psychological testing makes it possible almost always to differentiate between organic and psychogenic disturbances. Pneumoencephalography and electroencephalography in selected cases, and when indicated, may uncover definite positive findings of structural and physiological change as a result of the trauma.

These are the patients who require special consideration for their specific handicaps and are potential candidates for prolonged rehabilitation handling. Their worries about cure, livelihood, bodily helplessness and future disturbances of social and economic nature are real and offer a tremendous challenge and appeal for life in the future without dependency on the family or the country.

Another clinical picture presented by effects of injury to the cerebrum by concussion, shell, bomb or other explosion is that associated with subdural hematoma or effusion. The picture here is quite different qualitatively from the psychoneurosis with anxiety or hysterical states encountered after head injury. In the latter, extreme restlessness, motor activity, tension, nightmares and insomnia are prevalent. Noises, sounds of airplane motors, exhaust explosions are triggers sending them into profound anxiety. The subdural cases, to the contrary, present one of two syndromes.

In the most frequent syndrome there is marked retardation in intellectual activity and personality interrelationships. The facies is one of dulness with but little play of facial expression. The emotional tone is flat. Attention is impaired and responses are slow. Answers to questions are devoid of description and detail. The whole approach to life situations is one of superficiality and getting by without complicated mental activity. The patient may or may not complain of headaches but he is usually not dramatic in his complaints.

The less frequent syndrome occurs in those cases of subdural hematoma of longer duration and demonstrates the more classic picture usually associated with the organic reaction types. The most striking feature is the impairment of inhibition or restraint, producing a euphoric and sometimes facetious air. Motor restlessness with exaggerated mannerisms and gesticulations may be prominent. The emotional tone may be labile and explosive. There may be poor judgment, undue productivity, unusual expressions of hostility and lack of restraint. Definite organic intellectual defects in the form of distractability, memory fail-

ure, perseveration and repetition and circumstantiality may be present. Infrequent or minimal neurologic findings are the rule and as a result cases with subdural hematoma or effusion repeatedly are considered functional. Pneumoencephalography and psychological testing are often necessary for a final diagnosis and treatment by the neurosurgeons.

In yet another group there are the debatable cases where the relationship between head injury and mental disease is not so clear, other than that the trauma may serve as the immediate precipitating agent producing a delirium tremens, a schizophrenia, a neurosyphilis or manic depressive or other psychosis. A certain group of these mental changes bear only an indirect relationship to the trauma which acted as precipitant on a pre-existing psychopathic state rather than as the direct etiologic agent. On the other hand, there are a group of organic mental syndromes following brain injury that can be delineated as definite post-traumatic psychopathy in individuals who never had signs of psychopathic states before sustaining injury.

Before closing, a few remarks are in order concerning psychiatric aspects of peripheral nerve and nerve trunk injuries. Just as in cerebral trauma, injury to nerves may precipitate various types of neurotic behavior, either the organic consequences become the nucleus around which neurotic attitudes develop or latent psychoneuroses gain expression by the generalized effect of the trauma and the prolonged effects of convalescence, crippling and handicapping. The demands for capacity to adjust to new situations created in life by these handicaps may be very great. They may be influenced also by the phantoms that may follow amputations of either painless or painful character or may appear in unamputated paralyzed limbs deprived of sensation by injury to the nerves. These lesions force the realization in cases with amputations in accepting physiologically as well as psychologically the shortened limb. One of the great difficulties encountered in these cases is the failure to possess or develop a strong natural aptitude to elongate the limb at will in the use of tools very much like the individual who never succeeds in accepting or incorporating his artificial teeth. The competency of this aptitude for projection varies in different individuals, depending largely upon their stability and their inherent adaptive capacity.

SUMMARY

Out of the war-time experience have arisen certain facts for em-

phasia Many individuals developing disabling neurosis after head injury suffer from latent or active neurosis before exposure to military life or from neurosis incidental to the war experience The patient's history frequently gives evidence of previous neurosis, psychoneurotic and neuropathic traits, unsatisfactory sexual adjustment, marked mood swings, seclusiveness, schizoid characteristics, extreme rigidity, excessive timidity, childhood fears, parental dependence, asocial acts, and previous psychological traumata Individuals with such characteristics in their make-up should not be considered for either military or civil assignments where the elements of special danger and personal physical risks are great Industry can well afford to profit by methods of selection of prospective employees for such jobs and positions similar in purpose to those used by the armed forces in selection of personnel for highly dangerous and hazardous undertakings, specifically such as in the flying and submarine branches of the service Even if a psychiatric staff cannot be employed or provided, the development of psychologist selection staffs should be encouraged The specific psychological tests and appraisals now available leave no excuse for haphazard selection of such employees

CONCLUSION

In conclusion, several valuable psychiatric factors have been introduced in the management of nervous system injuries by the experiences of this war Prophylactic psychotherapy during the management of the immediate post-traumatic phase had reduced persistent disability prospect Application of short term techniques of therapy based on psychoanalytic principles, followed by sound rehabilitation programs has been most helpful in the treatment of nervous system injuries with subsequent neurotic expressions Diagnostic and prognostic aids from psychological testing, electroencephalography and air encephalography may be necessary in the full appreciation of either structural damage or the psychoneurotic state Those cases with mixed pictures of organic and functional disturbances require management according to the merits of their particular cases, either by prolonged psychotherapy, programs of rehabilitation or by the protective environment of institutional life

THE PRESENT STATUS OF THE ETIOLOGY OF PRIMARY ATYPICAL PNEUMONIA*

COMMISSION ON ACUTE RESPIRATORY DISEASES**

JOHN H DINGLE, *Director*

PRIMARY atypical pneumonia has been well recognized as a distinct clinical entity during the past six years¹⁻³ Except in a small proportion of cases, the syndrome may be differentiated readily from the common bacterial pneumonias Epidemiological observations have been made of the disease under conditions of endemic and epidemic spread^{4,7} The possible relationship of atypical pneumonia and undifferentiated acute respiratory disease has been pointed out by several investigators^{8,7}

Although the clinical and epidemiological aspects of primary atypical pneumonia have been quite well characterized, much uncertainty and obscurity still exist with respect to the cause of this syndrome It has been recognized for some time that similar clinical illnesses may be produced by certain well-known agents The relatively minor role of such agents in the production of atypical pneumonia as seen today, however, has not been emphasized

We wish to present tonight a review of the present status of the etiology of primary atypical pneumonia and a summary of the studies carried out by the Commission on Acute Respiratory Diseases in an attempt to transmit this disease to animals and to human volunteers

ATYPICAL PNEUMONIA CAUSED BY KNOWN AGENTS

The clinical syndrome of atypical pneumonia may be produced in

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** Presented October 16, 1944 by John H. Dingle, Major, M.C., Director, before the Seventeenth Graduate Fortnight of The New York Academy of Medicine From the Respiratory Diseases Commission Laboratory, Regional Hospital, Section 2, Fort Bragg, North Carolina. Members and professional associates of the Commission on Acute Respiratory Diseases are John H. Dingle, Major, M.C., A.U.S., Director, Theodore J. Abernethy, Major, M.C., A.U.S., George F. Badger, Captain, M.C., A.U.S., Joseph W. Beard, M.D., Norman L. Cressy, Major, M.C., A.U.S., A. E. Feller, M.D., Irving Gordon, M.D., Alexander D. Langmuir, Captain, M.C., A.U.S., Charles H. Rammelkamp, Jr., M.D., Elias Strauss, Captain, M.C., A.U.S., and Hugh Tatlock, 1st Lieutenant, M.C., A.U.S.

its essential characteristics by a variety of agents, including bacteria, fungi, Rickettsia, and viruses^{1,3} An etiological diagnosis can be established in these cases by the use of procedures such as intradermal tests, isolation of the agent, and immunological or serological tests with the patients' acute-phase and convalescent-phase sera When positive results are obtained, the illness must be considered as a pneumonia of specific etiological type and the diagnosis of primary atypical pneumonia should not be employed In this respect, particular mention should be made of the psittacosis-lymphogranuloma or ornithosis group of viruses Several recent publications have indicated that these viruses cause many cases of so-called primary atypical pneumonia^{8,17} While there is no doubt that localized outbreaks as well as sporadic cases of pneumonia due to these agents can occur, the data now accumulating indicate that the great majority of cases of primary atypical pneumonia are not caused by the psittacosis or related viruses^{6,12,18} During the past three years of the Commission's experience in the Army, the diagnosis of psittacosis or ornithosis has not once been established in a series of more than 500 patients with atypical pneumonia and other respiratory infections

The bacteria, fungi, Rickettsia, and viruses known to produce pneumonia must therefore be sought and excluded as a cause of illness in any study of primary atypical pneumonia It now appears to be established, however, that all of these known agents taken together account for an exceedingly small proportion of the total number of cases diagnosed as primary atypical pneumonia, in civilian as well as in military populations

PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN CAUSE

Extensive investigations have been carried out during the past few years in a number of laboratories in an attempt to transmit primary atypical pneumonia of undetermined cause In most of the work laboratory animals of various species have been employed Isolation of the causative agent has been claimed or implied in several recent publications

Animal experimentation In 1939, Stokes, Kenney, and Shaw¹⁹ reported the transmission of a pneumotropic agent from the sputa of patients with atypical pneumonia to ferrets and mice Unfortunately the agent was lost after several passages in mice and its serological relationship to the patients' illnesses was not established The following

year Weir and Horsfall²⁰ reported the recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose. Experiments with other animal species yielded negative results. The specimens employed were obtained from patients whose illnesses were consistent with a diagnosis of primary atypical pneumonia. The agent could apparently be maintained in chick embryos without the production of lesions. On transmission in the mongoose, lesions were produced with some irregularity. Neutralization with convalescent sera of the patients could not be obtained on initial inoculation of serum-virus mixtures, but was evidenced from a lower percentage of lesions in the mongooses by serial passages, in contrast to the results when acute-phase serum-virus mixtures were employed.

It may be of significance that the above two investigations were carried out on cases occurring during a period when atypical pneumonia attracted the attention of physicians in several Eastern cities.²¹⁻²³ While it is likely that recognition alone accounted for the reported prevalence of the disease, it is also possible that the cases were unique etiologically.

In the past three years several other reports have appeared. Blake, Howard, and Tatlock²⁴ isolated a pneumotropic agent from cats ill concomitantly with human cases of atypical pneumonia in a single household. Neutralization tests, though incomplete, suggested that the human and feline illnesses might have been due to the same agent. Baker¹¹ likewise isolated an agent from feline pneumonia and suggested its causal relationship to human atypical pneumonia. Baker's agent, however, subsequently proved to be a virus of the psittacosis-lymphogranuloma group.^{15,25-26}

By the intranasal inoculation of cotton rats with sputa from cases of atypical pneumonia in the Army, Johnson⁶ obtained pulmonary lesions. On passage of the lungs of these animals, however, lesions failed to persist with any degree of constancy.

Eaton, Meiklejohn, Van Herick, and Talbot^{27,28} also found lesions in cotton rats and hamsters inoculated with sputa and lungs from patients with atypical pneumonia. More consistent results were obtained by the inoculation of chick embryos with material from the patients and subsequent inoculation of cotton rats and hamsters with the chick embryo tissue. Using this technique, it was found that convalescent sera from patients with atypical pneumonia prevented the production of lesions by the chick embryo tissue in most of the animals.

Horsfall and his coworkers²⁰ likewise obtained lesions by direct intranasal inoculation of cotton rats with sputa from certain cases of atypical pneumonia, but the lesions were not maintained on passage. These investigators further found that many of the animals, if permitted to survive, developed neutralizing antibodies for the pneumonia virus of mice.³⁰ Convalescent sera from patients with atypical pneumonia, when mixed with the sputum prior to inoculation, prevented the development of such antibodies, although these sera themselves contained no antibodies to the mouse virus. It was subsequently found³¹ that antibodies to the pneumonia virus of mice could be stimulated non-specifically in cotton rats by inoculation of substances such as broth. Thus the appearance of these antibodies may well result from evoking a latent virus, but the ability of convalescent atypical pneumonia sera to prevent the development of the antibodies remains an unexplained observation.

Rose and Molloy³² reported the occurrence of pulmonary lesions in newly-weaned guinea pigs inoculated intranasally with specimens from patients ill with atypical pneumonia. Immunological confirmation of the relation of such lesions to atypical pneumonia could not be obtained, however, and Rose³³ now holds the opinion that no causal association exists.

Sanders³⁴ has isolated a virus in tissue culture and mice from the sputum of a case of atypical pneumonia. The virus produces a fatal encephalitis in mice but fails to cause pulmonary lesions. A strain of this virus, kindly supplied by Major Sanders, has been studied in the Commission laboratory. The development of antibodies to this agent during the course of atypical pneumonia could not be demonstrated by the neutralization test in mice. The agent appears to be a variant of the herpes virus.

An unusual combination of immunological reactions can be demonstrated with convalescent sera from cases of atypical pneumonia. They are, first, cold hemagglutination, second, fixation of complement with a variety of dissimilar antigens, third, prevention of the development of antibodies to the mouse pneumonia virus, and last, agglutination of an indifferent streptococcus. In general, the reactions are found with greatest constancy in sera from the most severely ill patients.

The development of cold agglutinins for group O human erythrocytes in the sera of patients with primary atypical pneumonia has been reported by a number of investigators.³⁵⁻⁴⁰ The proportion of cases

showing this reaction has varied in different series from about 30 per cent to almost 100 per cent, depending in all probability on the factors of selection which entered into the availability of the cases. In an Army hospital, for example, a large number of patients with atypical pneumonia have such mild illnesses that they would not be hospitalized in civilian life. Thus far, no clues to the causative agent of atypical pneumonia have been afforded and substantiated by the reaction of cold hemagglutination.

Thomas and his co-workers⁴¹ have reported that the sera of certain patients convalescing from primary atypical pneumonia have the capacity to fix complement with a variety of antigens, particularly those consisting of fresh suspensions of tissue. Fixation occurred with suspensions of various organs from different animal species, regardless of whether the animals were normal or infected with one of several viruses. These results have been confirmed on a limited scale in the Commission laboratory.

The capacity of convalescent sera of cases of atypical pneumonia to prevent the development of antibodies to the pneumonia virus of mice in animals inoculated with sputum²⁹ has already been discussed.

In 1943, Thomas and his co-workers⁴²⁻⁴³ at the Rockefeller Institute reported the isolation of an indifferent streptococcus from lungs and sputa of certain cases of primary atypical pneumonia. This organism is agglutinated by convalescent-phase sera from some patients with atypical pneumonia. It is closely related immunologically to *Streptococcus salivarius*, type I⁴⁴ and owes its serological reactivity primarily to a capsular polysaccharide. The organism in pure culture is not pathogenic for experimental animals. Cross-adsorption tests have shown that the agglutinins for the streptococcus are distinct from cold agglutinins for human group O erythrocytes. At the present time, the role of the bacterium in the causation of primary atypical pneumonia is obscure.

The convalescent sera of many cases of primary atypical pneumonia thus have the capacity to react immunologically in a variety of ways and with grossly dissimilar antigenic substances. While it is possible that these substances all have antigens in common with the causative agent of atypical pneumonia, yet another tenable hypothesis is that the various reactions reflect an alteration in the serum proteins and their reactivity, which is demonstrable non-specifically.

Repeated attempts to detect or isolate the causal agent or agents of

primary atypical pneumonia have been made in the Commission laboratories during the past three years. Throat washings, sputa, and blood from more than sixty cases of atypical pneumonia have been utilized. In addition, lung, spleen, brain, and other tissues from six fatal cases have been studied. In so far as possible, bacteria, fungi, Rickettsia and known viruses were sought for and excluded as causative agents in these cases.

Throat washings, sputa and lung have been subjected to fractional ultracentrifugation. The various fractions so obtained have been used in animal experiments as inocula, and in complement-fixation tests as antigens with acute-phase and convalescent-phase sera from cases of atypical pneumonia. The results failed to indicate the presence of any specific agent. Examination of the fractions with the electron microscope revealed no characteristic particles not also found in control specimens.

Extensive animal experimentation has been done, employing various routes and methods of inoculation, with and without adjuvants, such as mucin. No agents which could be related definitely to the human disease have been isolated in chick embryos, chickens, doves, Java rice-birds, mice, guinea pigs, ferrets, rabbits, dogs and three species of monkeys. Similar negative results were obtained with cotton rats and kittens. A series of experiments⁴⁵ employing the mongoose as the experimental animal has been carried out in the Antilles Department Medical Laboratory in Puerto Rico with the collaboration of Major G. J. Dammin and Captain T. H. Weller. Throat washings from seven cases of primary atypical pneumonia, sputa from six cases, lung from two fatal cases, and control specimens were inoculated intranasally and passed serially in a total of 265 mongooses. An agent was not isolated, nor could clinical or pathological evidence of pulmonary infection be demonstrated in these animals.

A great deal of the animal experimentation in the Commission Laboratory has been difficult to interpret due to the occurrence of non-specific or spontaneous pulmonary lesions following intranasal inoculation and passage. At times, latent agents which could be identified have been evoked, such as the pneumonia virus of mice and viruses of the psittacosis-lymphogranuloma group. At other times, lesions have appeared in one passage, only to disappear completely on subsequent passage of those lungs. Extensive controls have been employed and in no instances have lesions appeared following inoculation of material from

patients with atypical pneumonia, which could not be duplicated in control series

Thus, the occurrence of non-specific lesions and possibly the evocation of latent agents may account for much of the confusion and conflicting reports in the literature regarding the causative agent of primary atypical pneumonia. At all events, it would appear that detailed control series must be employed at all stages in animal experimentation—not only for attempting isolation of an agent, but also for relating the agent so obtained to the human disease.

Human experimentation In view of the equivocal results in animal investigations, it seemed desirable to study experimentally the transmission of primary atypical pneumonia in the natural host, man. One such study has been reported. Vance, Scott, and Mason⁴⁶ were unsuccessful in transmitting the disease to seven volunteers by intranasal inoculation with filtrates of sputa and nasal washings.

The experiments summarized below have been carried out in human beings to determine (a) whether or not the disease is transmissible with secretions of the respiratory tract of ill patients, and (b) whether or not bacteria-free filtrates of such secretions are capable of inducing infection. The subjects were conscientious objectors who volunteered after the nature of the investigation had been completely explained to them.

The first experiment⁴⁷ was conducted in October, 1943, in a Civilian Public Service camp near Gatlinburg, Tennessee. A roentgenographic survey of the entire personnel of the camp failed to reveal any cases of atypical pneumonia. Accordingly, fifteen volunteers were placed in group isolation in the camp's infirmary. During the next five days, the men were examined daily for evidence of respiratory disease. Three individuals developed mild, afebrile upper respiratory infections during this time and were not inoculated. None of the three developed evidence of pulmonary involvement at this period or subsequently. Despite this complication, the remaining twelve men were inoculated with a pool of untreated sputa and throat washings from seven cases of atypical pneumonia. The sputa and throat washings were mixed and sprayed from an atomizer and nebulizer into the nose and pharynx of each volunteer, synchronizing the spraying with his inhalations.

Respiratory illnesses developed in ten of the twelve volunteers inoculated. These illnesses varied in their clinical characteristics, severity, and course. In two of the men the infections were mild without fever

In the remaining eight cases, fever developed from approximately 7 to 22 days after the inoculations. Three of the eight showed no evidence of pneumonia at any time, but characteristic "sticky," subcrepitant rales were present in the lungs of 5 patients. The roentgenograms of three of these patients showed minimal patchy infiltration in one or both lower lobes, and their illnesses were consistent clinically with moderately severe atypical pneumonia. The illnesses of the other two patients were similar to those considered as "suspected atypical pneumonia" or "bronchitis resembling atypical pneumonia," in that the clinical illness and physical signs were characteristic of atypical pneumonia, but pulmonary infiltration was not demonstrable roentgenographically. The sera of three of the men showed cold agglutinins in titers of 64, 128, and 256, respectively, during the course of their illness. None of the patients developed agglutinins for the indifferent streptococcus or antibodies for the influenza viruses.

These preliminary results were encouraging, even though interpretation was complicated, first, by the occurrence of mild respiratory infections in three of the group before the time of inoculation, secondly, by the possibility of cross-infection among the twelve inoculated men, and, lastly, by the failure of any of them to develop pronounced pulmonary infiltration. None the less, the illnesses of three of the men, following inoculation, were clinically characteristic of atypical pneumonia, and no similar illnesses occurred in the other personnel of the camp during the period of the experiment. Moreover, the infections were neither similar to the common cold clinically,⁴⁸ nor to influenza clinically and immunologically.

The second experiment was carried out in June and July, 1944. Thirty-six volunteers were placed in isolation in individual rooms equipped with private baths on the 2nd and 3rd floors of a 75-room hotel. Quarantine was instituted to prevent chance exposure to atypical pneumonia through outside contact, and was maintained for a period of three weeks prior to inoculation, since the available evidence suggested this interval as the maximal limit of the incubation period. The usual isolation techniques of a contagious hospital were instituted and maintained. Complete examinations, including roentgenographic, electrocardiographic and laboratory studies were done. The men were observed on alternate days for symptoms and signs of respiratory infection. Any one with acute or chronic organic or infectious disease was rejected.

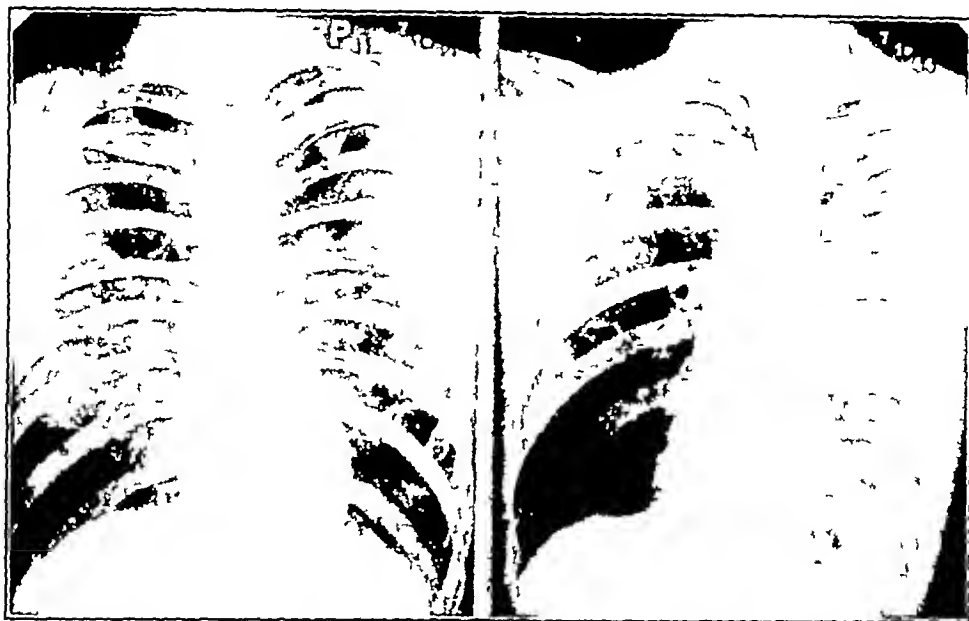
After three weeks of isolation and observation, the men were inoculated in three groups of twelve persons each, as follows (a) untreated throat washings and sputa pooled from seven cases of primary atypical pneumonia, (b) the same material, filtered through sintered glass and Seitz filters, and (c) the same material, autoclaved. The inoculations were made on a single day, utilizing first floor rooms located in one wing of the hotel as remote from the rooms of the volunteers as was possible. Three separate rooms, on the same side of the hall, were employed for the three types of inocula. Sheets, wet with cresol solution, were hung over the doors outside the rooms. The doors were opened frequently to admit entrance or exit of the volunteers and investigators.

Each man received a total inoculum of 10 ml administered in three equally divided doses by spraying in synchronization with deep inhalation. The material was sprayed by three methods: hand atomizer, hand nebulizer, and an atomizer powered by a motor-driven air pump—the power spray commonly employed by otolaryngologists. The power spray was used first for the filtered material, secondly for the autoclaved material, and finally for the untreated inoculum. The equipment was sterilized between each set of inoculations, with the exception of the inner surface of the air pump on the power spray which was overlooked. The volunteers and professional personnel were masked and gowned in an attempt to prevent cross-infection or extraneous exposure. Precautions were taken to insure consistency and comparability in the inoculations of the three groups of men.

Ten cases of atypical pneumonia developed among the thirty-six volunteers. The cases varied in severity but all were characteristic of the disease as it has occurred in the Army. The following charts and brief case summaries will illustrate the essential character of the clinical illnesses and radiographic findings.

Cold hemagglutinin titers of 64 or greater developed in the sera of seven of the ten cases of atypical pneumonia during the course of illness. Agglutinins for the indifferent streptococcus, Rockefeller strain No. 344, developed during convalescence in the sera of two cases in a maximum titer of 32 from a pre-inoculation titer of <8 . No change in titer was detected in the other eight cases.

Repeated attempts were made to isolate the indifferent streptococcus by culture from the volunteers both before and after inoculation. The organism was found in one-third of the men before inoculation and in



JULY 10

JULY 10

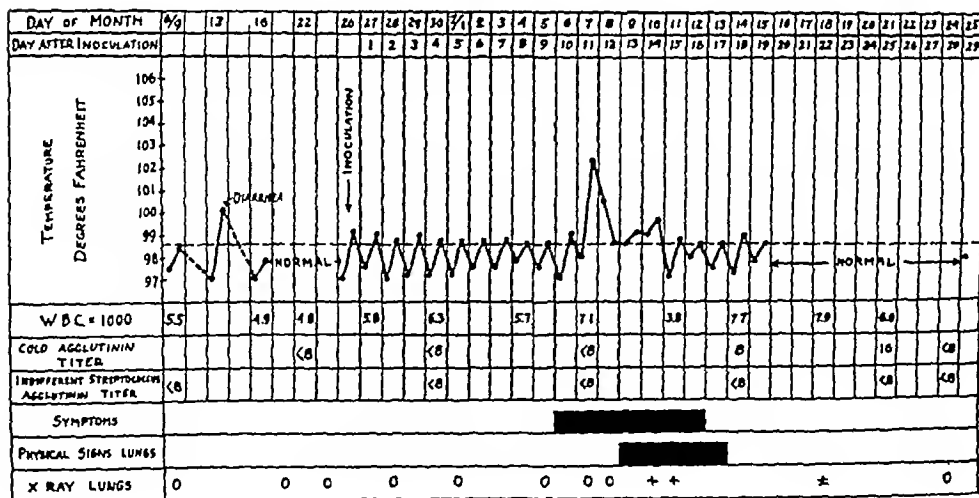


Figure 1—A mild case of primary atypical pneumonia. This patient experienced a mild episode of gastro-enteritis during the period of quarantine. Recovery was prompt and complete. On the tenth day after inoculation he developed mild atypical pneumonia, demonstrable by roentgenogram, in the left lower lung field. Cold hemagglutinins and agglutinins for an indifferent streptococcus (#344) did not develop (Case No 46).



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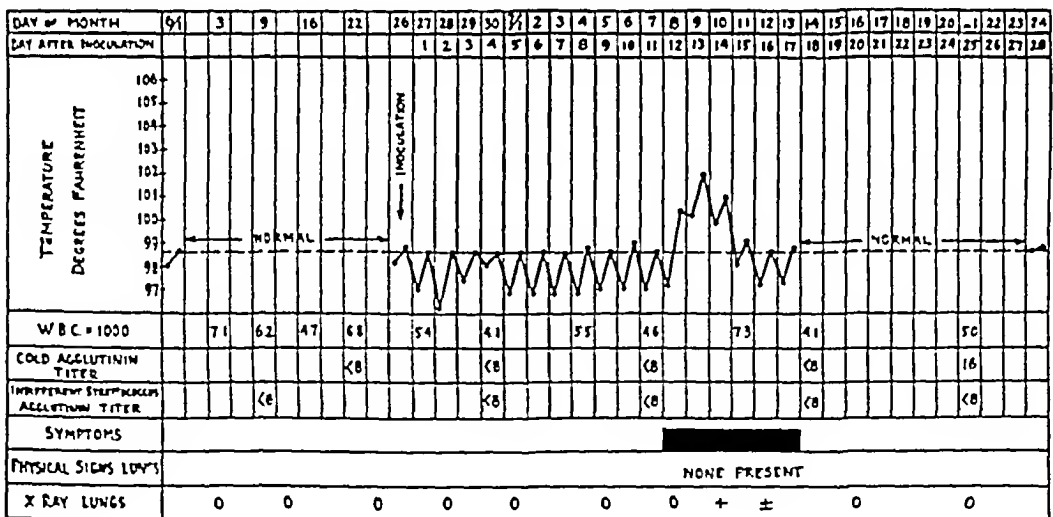


Figure 2—(Case No. 25) A mild case of primary atypical pneumonia. Mild atypical pneumonia began abruptly in this patient 12 days after inoculation. Roentgenogram on the 14th day (July 10th) showed a soft infiltration in the left lower lobe. No abnormal physical signs in the lungs were detected at any time. Neither cold hemagglutinins nor agglutinins for streptococcus 2344 were detected in his convalescent sera.



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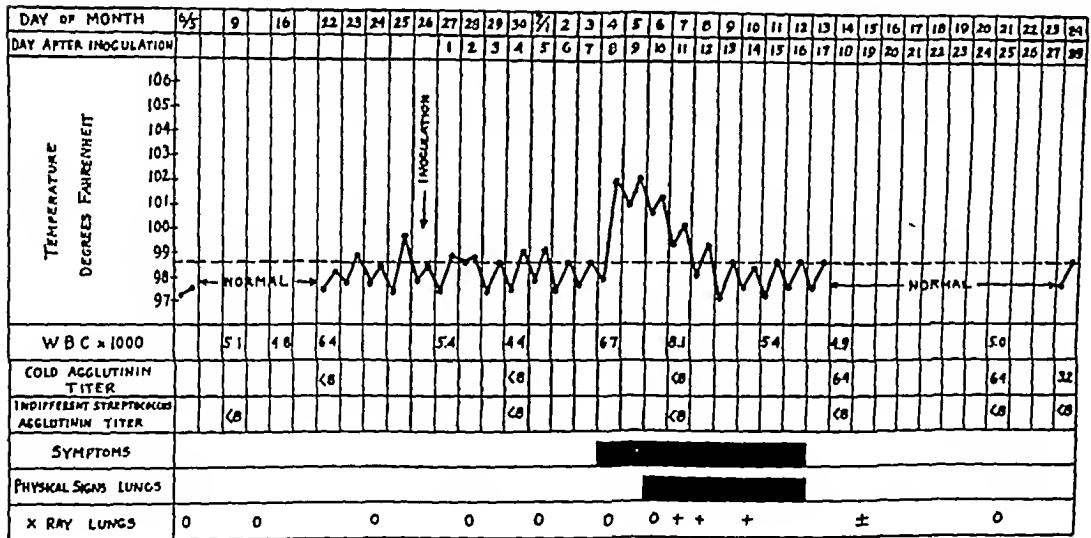


Figure 3—(Case No 42) A mild case of primary atypical pneumonia with pulmonary infiltration visualized roentgenographically only in the right and left oblique positions. This patient experienced a mild attack of atypical pneumonia beginning on the 8th day after inoculation. Physical signs of pulmonary involvement were present in both bases. Areas of infiltration at the extreme lung bases were visualized roentgenographically only in the right and left oblique positions and were not visible in the conventional posterior-anterior films. Convalescent sera showed a maximum cold hemagglutinin titer of 64, agglutinins for the indifferent streptococcus were not found.



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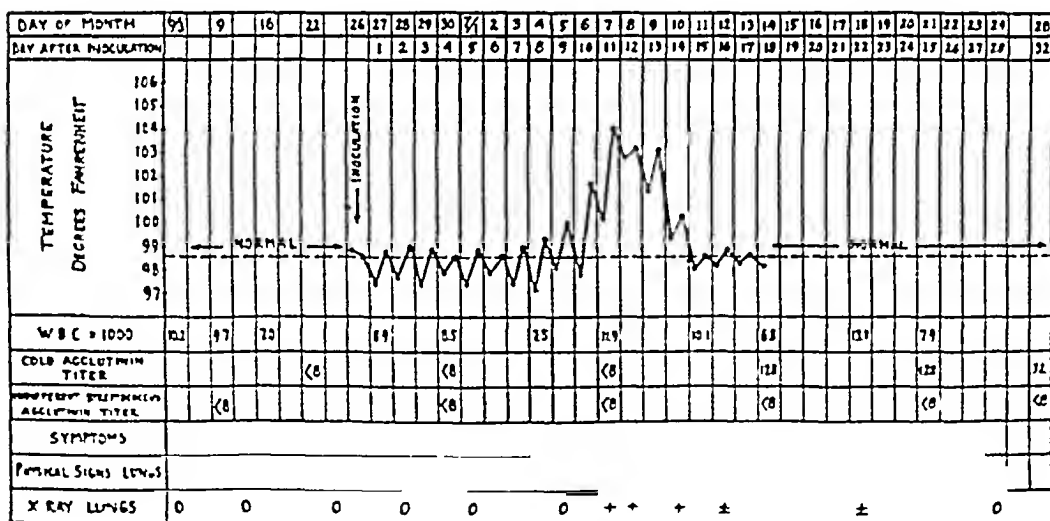


Figure 4—(Case No. 2) A moderately severe case of primary atypical pneumonia with involvement of the entire right lung and left lower lobe. Moderately severe atypical pneumonia developed in this patient 8 days after inoculation. The infiltration ultimately involved the entire right lung and the left lower lobe. Cold hemagglutinins developed to a titer of 128. No agglutinins for the indifferent streptococcus were demonstrable.



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JULY 24

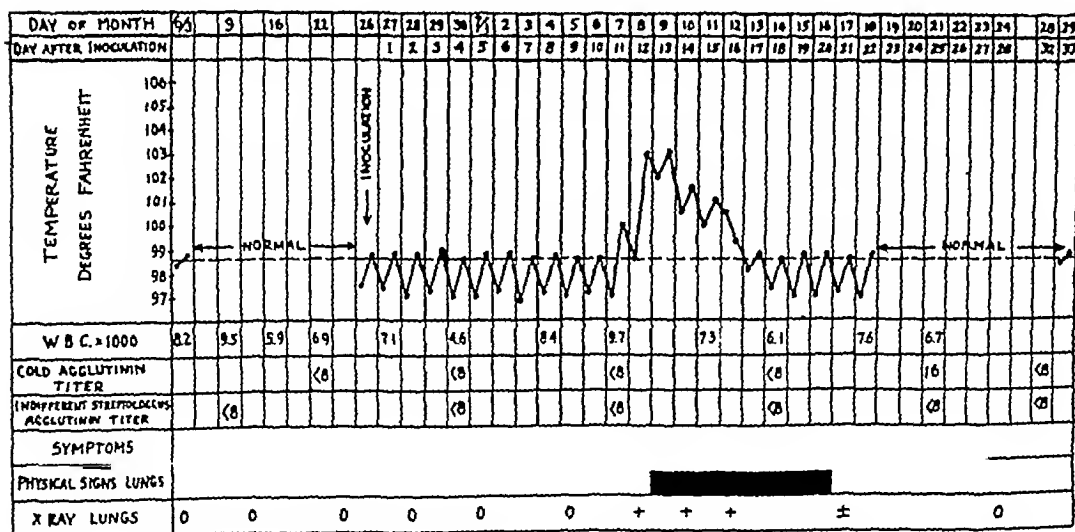


Figure 5—(Case No. 5) A moderately severe case of primary atypical pneumonia. This patient experienced moderately severe atypical pneumonia. Symptoms appeared 8 days after inoculation and the temperature became elevated 3 days later. Pneumonic infiltration appeared first in the left lower lobe and subsequently involved the right lower lobe. Abnormal physical signs were present at both bases. Neither cold hemagglutinins nor agglutinins for streptococcus #344 were found in the convalescent sera in significant titers.



JULY 11

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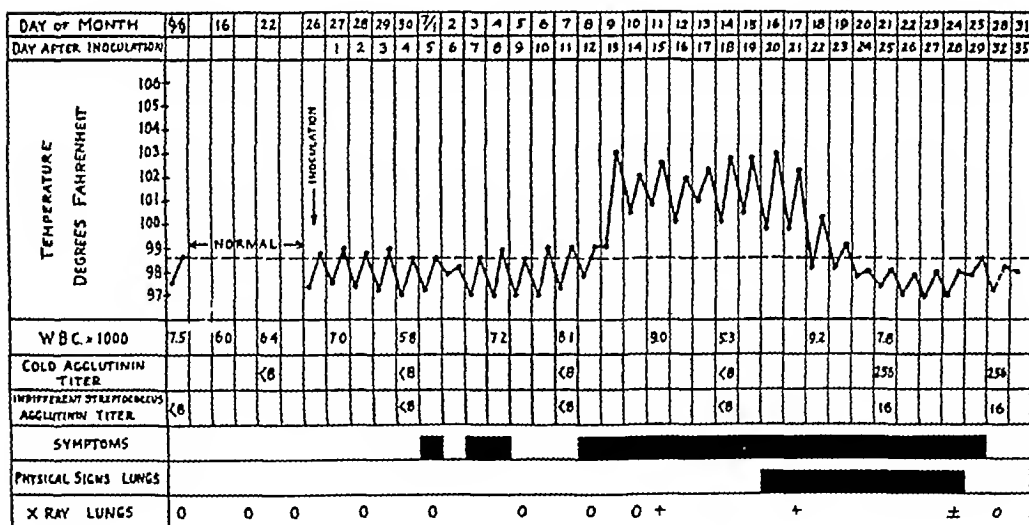


Figure 6—(Case No. 45) A moderately severe case of primary atypical pneumonia. After 2 intermittent periods of respiratory symptoms, this patient became ill with moderately severe atypical pneumonia on the 12th day, post-inoculation. Remittent fever persisted for 10 days. Patchy pneumonic infiltration of the entire right lung and left lower lobe were demonstrable in roentgenograms. Cold hemagglutinins were present in a maximum titer of 256 on the 25th day after inoculation, or 13 days after onset of illness. Streptococcus agglutinins increased to a titer of 16 at the same time and reached a titer of 32, 4 weeks later.



JULY 15

JULY 15

JULY 15

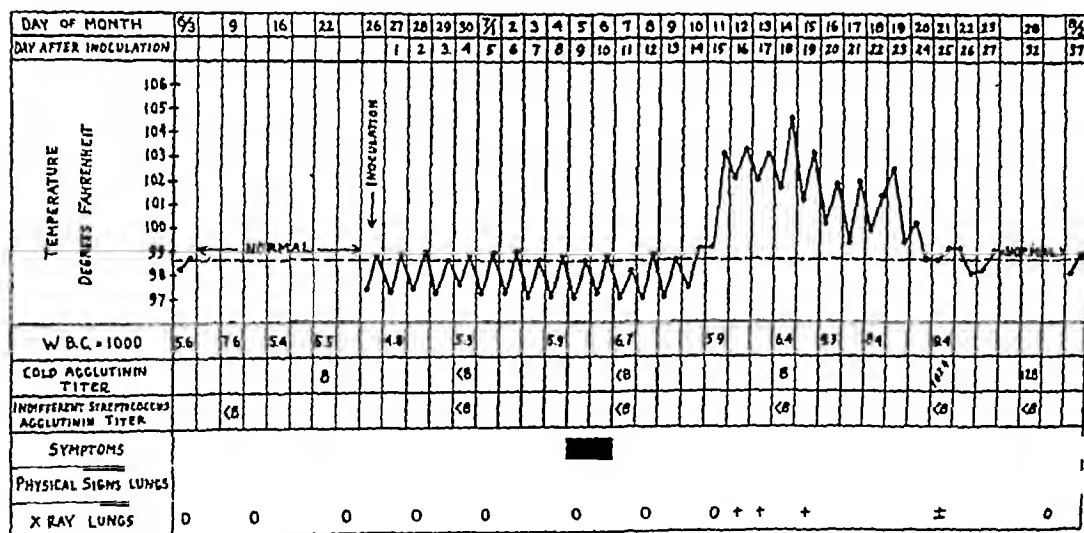
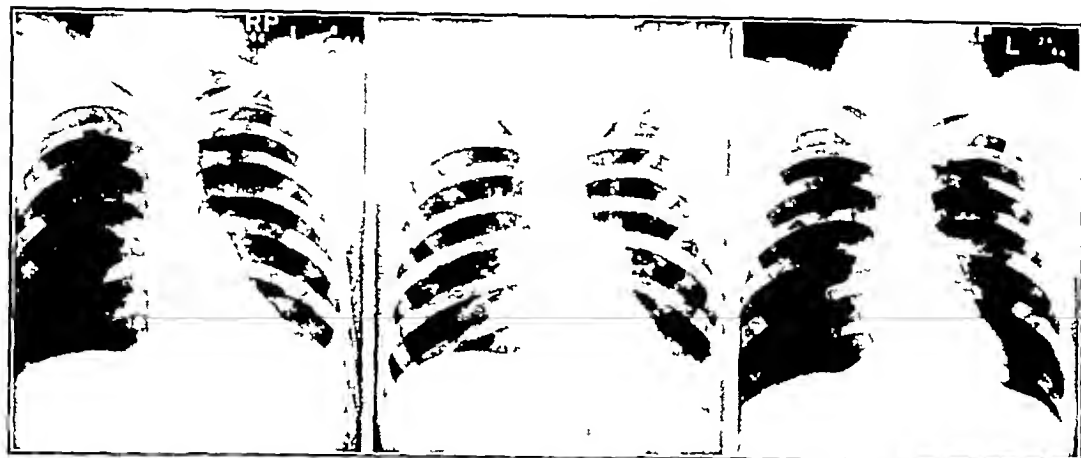


Figure 7—(Case No 24) A severe case of primary atypical pneumonia complicated by disorientation and emotional instability. This patient's illness was characterized by high temperature and patchy infiltration at both lung bases on July 15th, the 19th day after inoculation. He was considerably sicker than the extent of his lesions would suggest. Following the peak of temperature of 104.6° F, disorientation and emotional instability were conspicuous features of his illness. Neurological examination revealed no abnormal findings, however, and the cerebrospinal fluid was normal. Recovery was complete. Cold hemagglutinins were demonstrable in a titer of 1024 on the 11th day after onset of illness. Agglutinins for streptococcus #344 were not found.



JULY 24

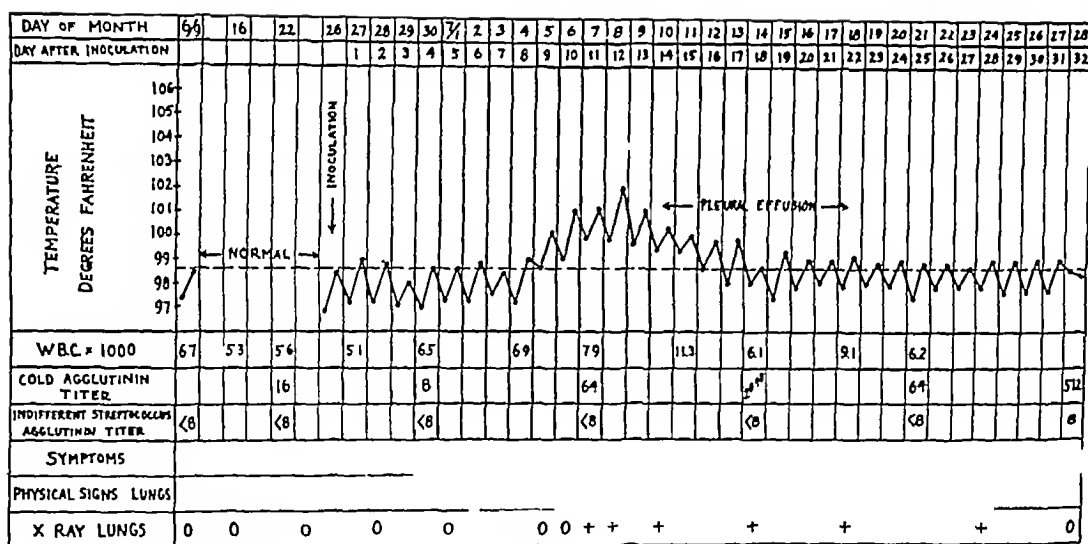


Figure 9—(Case No. 44) A relatively mild case of primary atypical pneumonia complicated by sterile pleural effusion. In this volunteer, atypical pneumonia, though relatively mild in character, was complicated by the development of pleural effusion at the left base. The fluid was sterile, greenish-yellow in color, and contained 1370 leukocytes and 240 erythrocytes per cubic millimeter. Approximately 55 per cent of the leukocytes were large mononuclear cells, the remainder were lymphocytes and neutrophils. Cold hemagglutinins were present in the patient's serum in a maximum titer of 2048. Agglutinins for streptococcus #314 were not present in significant titer.



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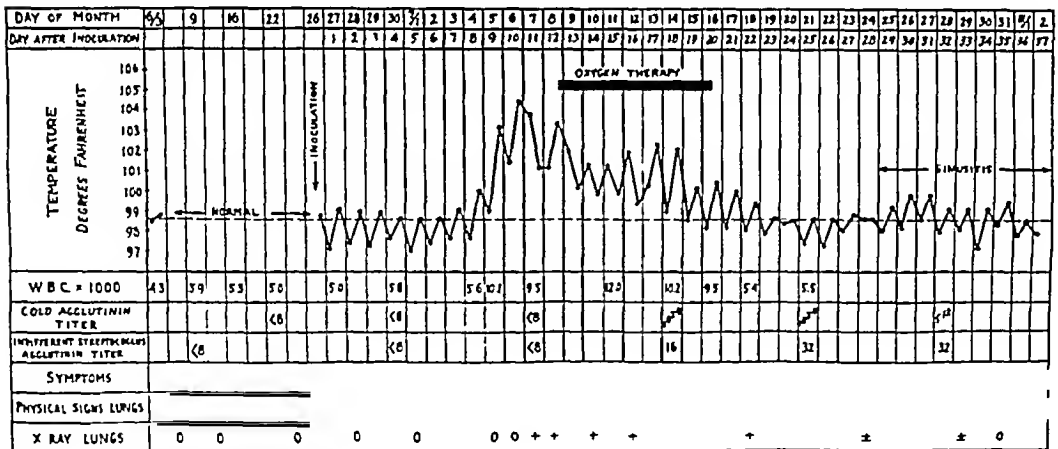


Figure 10—(Case No. 4) A severe case of primary atypical pneumonia with involvement of all lobes of the lung. This case represents the most severe atypical pneumonia in the group. Pulmonary infiltration appeared first in the right upper and middle lobes and subsequently extended to involve all five lobes. By roentgenogram a fine diffuse mottling was present throughout the lung fields. Oxygen therapy was required for approximately a week. Sinusitis occurred as a complication. Recovery was gradual but ultimately complete. Cold hemagglutinins and streptococcus agglutinins reached titers of 1024 and 32, respectively, in the convalescent sera.

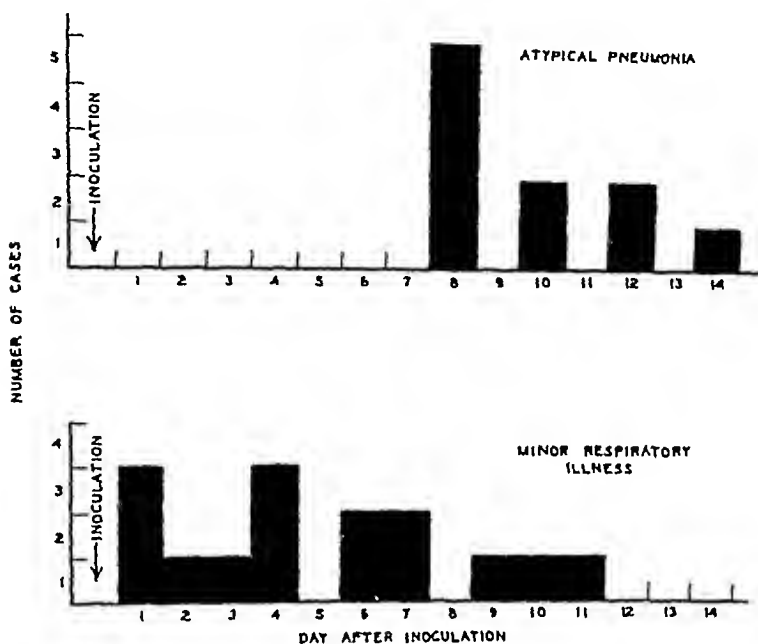
ONSET OF ATYPICAL PNEUMONIA AND
MINOR RESPIRATORY ILLNESS

Figure 11

one-half of them after inoculation, but the increase occurred with equal frequency in those who developed atypical pneumonia and in those who did not. There was, therefore, no apparent relation between the presence of this organism, either before or after inoculation, and the development of atypical pneumonia.

In addition to the ten cases of primary atypical pneumonia, there were fifteen cases of minor respiratory illness of undifferentiated type. The clinical onset of these cases, as well as that of the cases of atypical pneumonia, in relation to inoculation is shown in figure 11. For the purpose of this chart, the clinical onset of atypical pneumonia was defined as the day of development of *persistent* symptoms or signs which resulted in atypical pneumonia. The clinical onset of minor respiratory illness was defined as the day of development of any recognizable symptom or sign which was a definite departure from the normal state for that individual but did not lead to atypical pneumonia. This distinction was necessary because many of the minor respiratory illnesses were of short duration.

The clinical onset of atypical pneumonia, as thus defined, varied

TABLE I

PRODUCTION OF PRIMARY ATYPICAL PNEUMONIA AND MINOR RESPIRATORY ILLNESS IN HUMAN VOLUNTEERS INOCULATED WITH UNREATED, FILTERED, AND AUTOCLAVED SPUTA AND THROAT WASHINGS FROM HOSPITALIZED CASES

<i>Inoculum</i>	<i>No Men</i>	<i>RESULT</i>		
		<i>AP</i>	<i>MRI</i>	<i>No Illness</i>
Untreated	12	3	9	0
Filtered	12	4	5	3
Autoclaved	12	3	1	8
Total	36	10	15	11

AP—Primary atypical pneumonia

MRI—Minor respiratory illness of undifferentiated type

from 8 to 14 days after inoculation, whereas the onset of minor respiratory illness varied from one to eleven days. If the criteria used for minor respiratory illness were applied to the cases of atypical pneumonia, however, the onset of illness was between one and twelve days after inoculation. Whether or not these results indicate the presence of multiple agents capable of causing respiratory illness or merely mild illnesses or prodromata due to a single agent, cannot be determined at present. In none of the cases was there any change in bacterial flora, after inoculation or during illness, to suggest causation or even secondary bacterial infection. No serological evidence was obtained indicating infection with a virus of the psittacosis-lymphogranuloma group.

The results of this experiment clearly indicated that primary atypical pneumonia, and in addition, minor undifferentiated respiratory illness could be transmitted with secretions of the respiratory tract of patients with atypical pneumonia. Further analysis of the results, however, revealed that atypical pneumonia was apparently produced without regard to the type of inoculum (Table I), that is, three cases occurred with untreated inoculum, four with filtered inoculum, and three with the autoclaved material. The production of minor respiratory illness indicated greater specificity in that nine cases occurred with untreated

inoculum, five with filtered material, and only one with autoclaved inoculum. The interval between inoculation and onset of illness was in general shortest in the group receiving untreated sputa and throat washings

A detailed review of all the conditions and procedures of the experiment was then undertaken in the hope of finding an explanation for the results. Numerous possibilities were considered but the three most likely explanations appeared to be (a) air-borne infection in the hallway on the day of inoculation, (b) contamination of the inner surface of the air pump for the power spray, and (c) the non-specific evocation of a latent agent. In support of air-borne infection was the occurrence of atypical pneumonia in an attendant who assisted in inoculating twelve volunteers with the untreated inoculum. Contamination of the air pump of the power spray could have been at least a contributing factor. During its first use with filtered inoculum, the air taken into the pump undoubtedly contained air-borne particles which were deposited on the inner surface of the pump. These particles could again have been liberated when the power spray was used with the autoclaved material. It is perhaps significant in this respect that, of the twelve men receiving autoclaved material, the three who developed atypical pneumonia were the first, second, and fourth in order of inoculation with the power spray. The possibility of non-specific evocation of a latent agent could only be determined by repetition of the experiment using extreme precautions against air-borne or other types of inadvertent "cross-infection."

The third experiment was then begun in August, 1944 as a repetition of the second, but with the following differences

- a The inoculum consisted of pooled sputa and throat washings from 6 cases of atypical pneumonia in the second experiment, thus providing an opportunity for passage of the agent
- b The inoculations were performed out-of-doors
- c A tank of nitrogen was used as a source of pressure in place of the motor-driven power spray
- d An interval of four days was allowed to elapse between inoculation of the autoclaved material and the filtered material. A second interval of 8 days elapsed before administration of the untreated inoculum
- e Eighteen men were included in the group which received auto-

TABLE II

PRODUCTION OF PRIMARY ATYPICAL PNEUMONIA AND MINOR RESPIRATORY ILLNESS IN HUMAN VOLUNTEERS INOCULATED WITH UNREATED, FILTERED, AND AUTOCLAVED SPUTA AND THROAT WASHINGS FROM EXPERIMENTALLY PRODUCED CASES OF ATYPICAL PNEUMONIA

<i>Inoculum</i>	<i>No Men</i>	<i>RESULT</i>		
		<i>AP</i>	<i>MRI</i>	<i>No Illness</i>
Untreated	12	3	5	4
Filtered	12	3	5	4
Autoclaved	18	0	1	17
Total	42	6	11	25

AP—Primary atypical pneumonia

MRI—Minor respiratory illness of undifferentiated type.

claved material to increase the possibility of demonstrating the evocation of a latent agent, if such were the cause

f The groups of men were segregated geographically within the building by construction of temporary partitions in the hallways. In other respects, the essential conditions of the experiment were the same.

Six cases of atypical pneumonia and eleven cases of minor respiratory infection occurred in this experiment. Three of the cases of minor respiratory infection were diagnosed as "suspected atypical pneumonia" or "bronchitis resembling atypical pneumonia," because of the characteristic clinical course and physical signs, without roentgenographic evidence of pulmonary infiltration. In general, the illnesses were somewhat less severe than those in the preceding experiment, but in other respects they were entirely characteristic.

Distribution of the cases with respect to type of inoculum is shown in Table II. The untreated material produced three cases of atypical pneumonia and five cases of minor respiratory illness of which two were instances of "suspected atypical pneumonia." In the group of men receiving filtered material, there were likewise three cases of atypical pneumonia and five cases of minor respiratory illness, but only one of

the latter could be diagnosed as "suspected atypical pneumonia." There were no cases of atypical pneumonia among the eighteen men inoculated with autoclaved material, and only one instance of minor illness. This case occurred in the only man, to our knowledge, who broke isolation. On at least one occasion, he descended the fire escape to the room below which was occupied by a volunteer who subsequently developed a minor respiratory illness diagnosed as "suspected atypical pneumonia."

A striking difference was noted in the incubation period of the illnesses. The clinical onset of illnesses in the men receiving untreated material, with one exception (14 days), occurred between five and eight days after inoculation, whereas it was between nine and fifteen days, or almost twice as long, with the filtered inoculum.

The results of this experiment thus demonstrate that primary atypical pneumonia may be produced in human beings with filtered as well as untreated secretions of the respiratory tract of patients ill with this disease.

DISCUSSION AND SUMMARY

An attempt has been made to review the present status of the etiology of primary atypical pneumonia. While a small proportion of cases presenting this clinical syndrome are due to known bacteria, fungi, or viruses, the cause of the majority of them remains to be characterized and identified.

The results of animal experimentation are confusing and difficult to interpret, due in large part to the lack of a truly susceptible animal, as well as to the complications introduced by the occurrence of spontaneous diseases causing pulmonary lesions in the animals employed. No work has yet been reported, and confirmed by other investigators in the field, which describes the isolation in animals of an agent clearly related immunologically to the human disease.

The experiments in human volunteers, summarized here, demonstrate that respiratory disease has been induced by the administration of sputa and throat washings of patients with primary atypical pneumonia. The clinical types of disease varied from the mildest of undifferentiated respiratory illness to classical severe atypical pneumonia. Between these extremes were cases resembling atypical pneumonia in onset, course, and physical findings, but lacking roentgenographic con-

firmation of pulmonary infiltration. Such cases were entirely similar to those observed on the respiratory wards of Army hospitals and diagnosed as "bronchitis resembling atypical pneumonia" or "suspected atypical pneumonia." The varied types of respiratory disease produced in these volunteers thus are consistent with the hypothesis previously advanced on the basis of clinical and epidemiological observations,¹⁷ namely, that primary atypical pneumonia may be a severe form with pulmonary involvement of the same infection responsible for a large part of the more common, mild respiratory illnesses.

From these experiments some information may be gained regarding human susceptibility to respiratory diseases. Excluding the controls inoculated with autoclaved material, three-fourths of the men developed some type of respiratory illness and one-fourth had atypical pneumonia. In spite of the relatively large dose of 10 ml, one-fourth of the men had no illness whatsoever. Direct comparison of these figures, however, with attack rates observed in civilian and military populations is probably not justified because of lack of knowledge regarding minimal infecting dosage.

The question of the transmission of primary atypical pneumonia with bacteria-free filtrates of sputa and throat washings from patients with this disease was not easily answered. The results of the second experiment, in which atypical pneumonia was apparently produced with autoclaved inocula, permitted no conclusion regarding infectivity of the filtrates. They furthermore raised the question of non-specific evocation of a latent agent as the cause of the disease, as well as the possibility of inadvertent infection.

Accordingly, the third experiment was carried out utilizing extreme precautions against inadvertent infection and increasing to 18 the number of men in the control group, to strengthen the likelihood of detecting non-specific evocation. Sputa and throat washings from the previous experimental cases were employed as inocula to establish serial passage. The results demonstrated that primary atypical pneumonia could be induced with bacteria-free filtrates of sputa and throat washings as well as with the same inoculum before filtration. Autoclaved material however was without effect. It therefore appeared probable that the agent was filterable, that a latent agent was not evoked non-specifically, and that the cases following inoculation of autoclaved material in the prior experiment resulted from inadvertent infection. More-

over, from experimentally produced cases of atypical pneumonia, this illness as well as undifferentiated respiratory disease could again be transmitted to well individuals

The length of time between inoculation and onset of illness may be of some significance, since this interval was almost twice as long in the cases receiving filtered inoculum as in those inoculated with untreated material. It is possible that such an increase in the incubation period is a function of dosage, and that filtration caused a considerable loss of the infecting agent. Another explanation is that bacteria act in conjunction with a filterable agent in the production of this disease. The failure to detect changes in bacterial flora following inoculation and during illness does not support, nor does it completely exclude, this concept.

The study in human volunteers thus leads to the conclusion that primary atypical pneumonia is at least initiated, if not caused, by a filter-passing agent, presumably a virus.*

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CHEMOTHERAPY IN ACUTE UPPER
RESPIRATORY INFECTIONS *

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THE topic assigned to me for this evening's discussion is a difficult one, chiefly because sufficient time has not yet elapsed for a thorough investigation of the possibilities of chemotherapy in upper respiratory infections. I take "chemotherapy" to mean the use of sulfonamides and penicillin. It is true that the sulfonamides have been widely used in the treatment of acute upper respiratory infections, but there is still considerable controversy among practitioners both as to methods and indications for the use of these agents. Penicillin has so recently been released for general civilian use that comparatively little is known about its value in coryza, influenza and their complications. We do know that penicillin possesses certain advantages that render it superior to the sulfonamides. Against susceptible organisms its antibacterial action is many times more potent than that of the sulfonamides. At the same time, even when it is administered in full therapeutic doses penicillin is entirely free of significant toxicity for the host. Unlike the sulfonamides, it is not inhibited by pus or the breakdown products of tissue autolysis. We know of course that most primary upper respiratory infections are of virus origin. It is also a fact that the great majority of viruses, including those causing coryza and influenza, are not subject to control by sulfonamides nor by penicillin.

It has generally been assumed that the complications of coryza and influenza are caused by secondary bacterial invasion, and it is true that cultures from such secondary infections as sinusitis, otitis, mastoiditis and bronchitis regularly yield one or more of the prevalent pathogens of the pneumococcal, streptococcal or staphylococcal groups. However, we need more thorough investigation of the bacteriology of these secondary infections. It has always seemed to me quite likely that the coryza or influenza virus not only attacks the nasopharyngeal mucosa,

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but frequently invades the adjacent tubes and cavities as well, thus preparing the way for secondary infection by a sort of symbiotic process. If this hypothesis is correct, it would explain some of the disappointments incurred with attempts to prevent or cure these complications by chemotherapy alone.

Let us now consider some of these infections in more detail.

ACUTE CORYZA

The uncomplicated common cold is a mild infection caused by a filtrable virus which usually runs an afebrile course and clears up completely in four to seven days. Although it is generally recognized that virus infections are unaffected by sulfonamides, many practitioners and otolaryngologists have administered one of the sulfonamides to patients with the common cold with the idea of preventing complications. The practitioners have usually given the drug by mouth, the otolaryngologists have used a spray or powder locally in the nose or throat. Such procedure seemed quite rational and in individual cases the results often appeared to be beneficial. For example, Crowe and his associates¹ at Johns Hopkins Hospital treated a group of nurses with colds by spraying the throat and nasal passages with a 2.5 per cent sulfadiazine in 8 per cent ethanolamine solution (Pickrell's solution). In addition to symptomatic relief they observed a reduction in complications and a decrease in secondary bacterial invaders in the nasopharynx, particularly hemolytic streptococci. The nose and throat were sprayed from eight to twelve times a day for three days, and five to eight times a day for an additional three days. Some sinus involvement was noted in 30 per cent of the control group, whereas in individuals who were sprayed with sulfadiazine, sinusitis developed in only 9.7 per cent. Cough developed in 44 per cent of the controls, in only 8 per cent of the treated group. Some of the patients objected to the taste of the spray. Others complained of irritation of the skin around the external nares. Mild allergic symptoms developed in a small percentage of patients.

Rusk and van Ravenswaay² have recently published their results on the oral use of sulfadiazine in the treatment of acute febrile respiratory infections which were seen in a large Army station hospital during the winter of 1942-1943. Doses of drug (3.0 Gm. initially followed by 1.0 Gm. every four hours) similar to those used in pneumonia were admin-

istered until improvement occurred. In the 317 treated patients compared with 314 comparable controls the authors observed no significant difference in either the length of the febrile period or in the period of hospitalization. Contrariwise, Siegel³ observed decided differences with and without sulfadiazine in alternate groups of feebleminded children with acute febrile respiratory infections, to which such individuals are particularly susceptible. In this reported series the incidence of serious secondary infections and the duration of the febrile period were considerably lessened.

In the winter and spring of 1942 the writer, in collaboration with Major Norman Plummer and Wilson G. Smilie⁴ carried out some experiments on the use of sulfadiazine in the treatment of the common cold at the New York Hospital. The subjects of this study were all members of the personnel of the New York Hospital staff, including nurses, interns, orderlies and technicians. These patients were followed carefully with clinical examinations and nasal and pharyngeal cultures. Of these volunteers with acute respiratory infection, 48 received sulfadiazine by mouth for four days, while 24 received placebo tablets which could not be distinguished from the sulfadiazine tablets. Treatment was

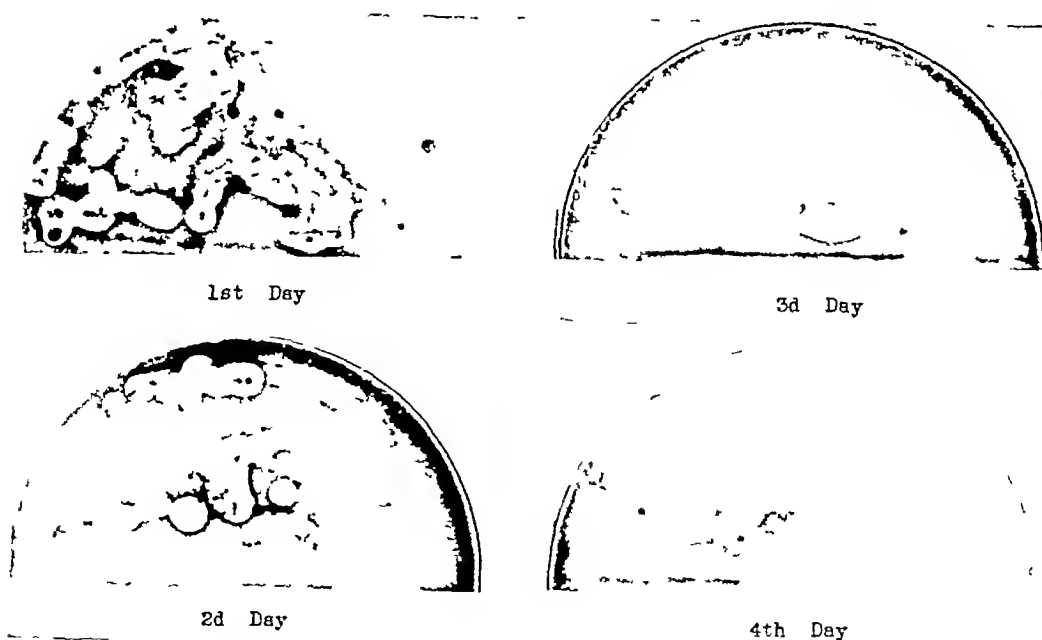


Fig 1—Decrease in normal nasopharyngeal flora following oral administration of sulfadiazine. Three grams daily for four days

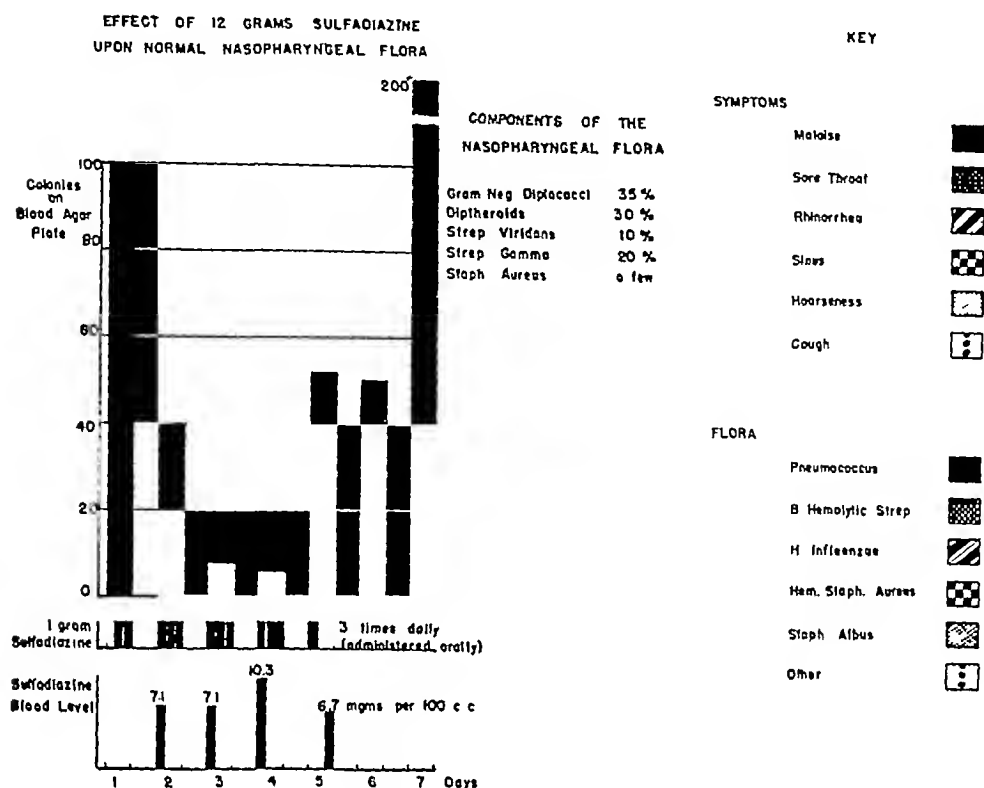


Fig 2—Effect of 12 Gm of sulfadiazine on normal nasopharyngeal flora

Fig 3—Key of symbols for symptoms and nasopharyngeal flora

usually initiated during the second or third day of the cold. Sulfadiazine was taken in oral doses of one Gm every eight hours for four days, or a total of 12 Gms. Nasopharyngeal cultures were taken at the time treatment was started and at regular intervals, usually every second to third day thereafter, in order to determine the changes that occurred in the nasopharyngeal flora following the treatment. Preliminary cultures on normal subjects indicated that on the dosage of sulfadiazine administered the blood level could reach 4-6 Mgm per 100 cc and that at this level there was pronounced reduction in the nasopharyngeal flora. Further cultures indicated a rapid return of the bacterial flora to its former prevalence and distribution within two to three days after sulfadiazine was discontinued.

Fig 1 illustrates on four blood agar plates marked reduction in the normal nasopharyngeal flora following oral administration of sulfadiazine, 3 Gms daily for four days.

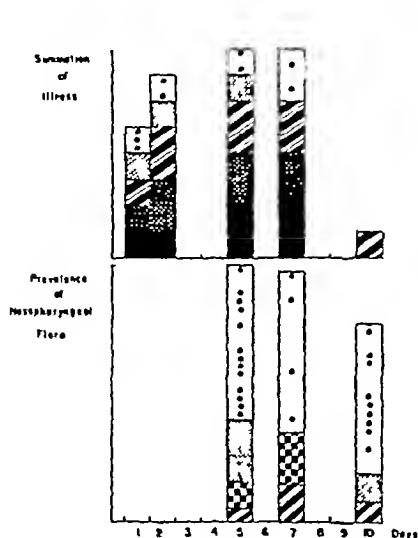


Fig 1—(MH) Control patient treated with milk sugar tablets. No change in pharyngeal flora, symptoms followed usual course

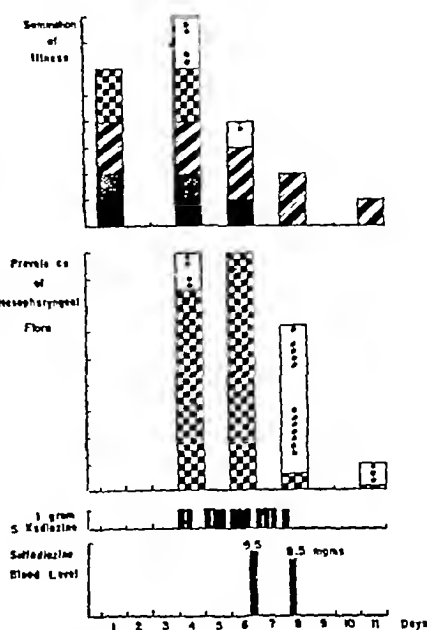


Fig 5—(GF) This patient shows a favorable clinical and bacteriologic response to sulfadiazine treatment

Fig 2 shows the total colony count and correlates it with the blood level of sulfadiazine. This chart also illustrates the rapid return of the organisms to their normal pattern after discontinuance of drug treatment.

Fig 3 is a key to the symbols used for designating the patient's symptoms and the character of the nasopharyngeal flora.

Fig 4 represents the course of symptoms and the nasopharyngeal flora in a patient with coryza who received no sulfadiazine, but had milk sugar tablets instead. On the day of onset the usual symptoms of malaise, sore throat, rhinorrhea, hoarseness and cough were present. These symptoms persisted and increased somewhat in severity. The pharyngeal flora remained unchanged during the ten days of observation.

In contrast to this case is the one represented by Figure 5, a patient with coryza who received sulfadiazine treatment. The symptoms cleared up on the 7th or 8th day, and there was a marked numerical drop in the nasopharyngeal flora.

Figure 6 shows a patient with coryza treated with sulfadiazine on the first day of the infection. There was a marked numerical drop in

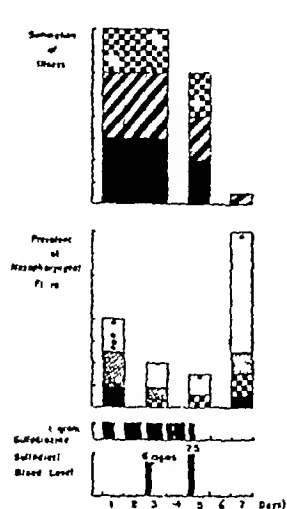


Fig 6—(B P) This patient shows excellent clinical and bacteriologic response to sulfadiazine but rapid re-appearance of bacteria after discontinuance of the drug

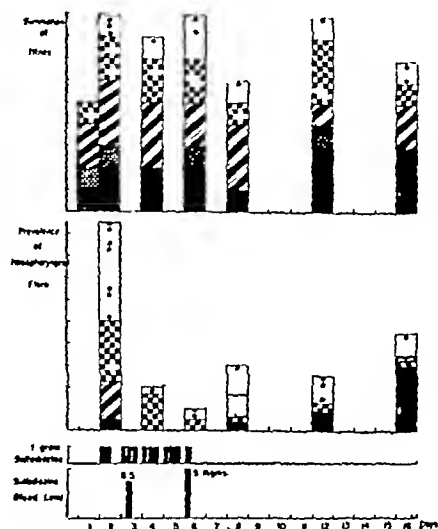


Fig 7—Acute coryza and sinusitis Patient showed good bacteriologic response to sulfadiazine with only slight clinical improvement With discontinuance of drug, pathogens again became numerous in the nasopharyngeal cultures, and patient developed a severe sinusitis and bronchitis

the nasopharyngeal flora, but the symptoms persisted for three days and then subsided slowly, disappearing almost completely on the 7th day. When treatment was discontinued, the number of organisms increased, although there was no return of symptoms.

Figure 7 (S M) is the graph of a case of acute coryza which started with an irritated throat followed by malaise, rhinorrhea and sinus congestion. Treatment was started on the second day, when the rhinorrhea was severe and there was also an irritative cough. The nasopharyngeal culture on this day showed a heavy growth with a few colonies each of beta hemolytic streptococcus, *H influenzae* and hemolytic *Staphylococcus aureus*. With the four days of treatment the course was somewhat favorable, the nasopharyngeal culture showing only a few organisms, the hemolytic streptococcus and *H influenzae* disappearing entirely, and the symptoms being slightly less in evidence. With cessation of sulfadiazine treatment, however, the hemolytic streptococcus returned and type 20 pneumococcus appeared in increasing numbers. At the same time the symptoms became aggravated and the patient developed a severe sinusitis and bronchitis. The suggestion in this case is that if chemotherapy had been continued for a longer period

the secondary infection might have been prevented

The illustrations cited above afford considerable evidence that sulfonamides do not alter the course of the uncomplicated cold. Furthermore, no outstanding benefits from sulfadiazine therapy were observed in colds complicated by sinusitis and bronchitis. It is quite clear, however, that secondary bacterial invaders can be eliminated or greatly reduced in number by sulfonamide therapy. Such being the case, it is rather surprising that sinus and bronchial complications would sometimes develop in the face of oral administration of sulfadiazine. Perhaps we made a mistake in not continuing the drug for longer than four days. The dosage used would certainly seem adequate, judging by the blood level.

Summarizing our clinical results, it must be admitted that they were not convincing. The average duration of the sulfadiazine-treated colds was 8.1 days, and that of the untreated colds 9.7 days. Of the 48 colds treated, 32 showed no recognizable secondary infection, 16 developed sinusitis, bronchitis or both, either during or after sulfadiazine treatment. Patients who developed complications, however, felt that they were milder in character than they would have been without the drug. The patients who received sulfadiazine were asked for their own opinions on the results obtained, and 34 expressed satisfaction with sulfadiazine treatment, 9 stated they noticed no difference from previous colds. The remainder had no opinion to offer.

ACUTE PHARYNGITIS AND TONSILLITIS

As far back as 1937 Long and Bliss⁵ reported favorably on the oral use of sulfanilamide in the treatment of pharyngitis and tonsillitis. On the other hand, Rhoads and Afremow⁶ in a controlled series of cases of pharyngitis and tonsillitis found that sulfanilamide did not lessen the severity of symptoms, reduce the incidence of complications or shorten the duration of the carrier state. Kernan⁷ found that sulfanilamide orally did not alter the ordinary course of tonsillitis, but that complications were fewer when it was used. It seems quite likely that penicillin will replace sulfonamides in the treatment of streptococcal pharyngitis and tonsillitis. For hemolytic streptococcus sore throats I see no particular point in giving either sulfonamides or penicillin unless the infection is severe. In the severe streptococcal throats, either sulfadiazine or penicillin should shorten and mitigate the attack.

Major Norman Plummer writes "We have had considerable experience with penicillin in the treatment of acute hemolytic streptococcal tonsillitis and pharyngitis. Undoubtedly penicillin is the superior drug against the hemolytic streptococcus and in conditions where there is an accumulation of pus"

ACUTE SINUSITIS

Otolaryngologists are pretty well agreed on the value of the sulfonamides in acute sinusitis, especially in the fulminating sinus infections which are often caused by the hemolytic streptococcus. Bowers⁸ prefers sulfadiazine or sulfathiazole powder applied directly to the mucous membranes. Silcox and Schenk⁹ have used a 5 per cent suspension of microcrystalline sulfathiazole for the treatment of acute and chronic sinusitis, the suspension being instilled directly into the sinuses. In addition to the differences of opinion over the relative value and safety of the different sulfonamides in their crystalline and liquid forms, the value and safety of oral versus local administration also remains controversial. Again, as in the case of tonsillitis and pharyngitis, it seems quite possible that penicillin will displace sulfonamides in the treatment of acute sinusitis.

CHRONIC SINUSITIS

In the treatment of chronic sinusitis there is considerable divergence of opinion on the value of sulfonamide drugs. Turnbull¹⁰ reported that a large proportion of patients with chronic sinusitis were benefitted by spraying the nasal cavities with a 5 per cent solution of sodium sulfathiazole. No untoward effects were observed in Turnbull's series of 47 cases. This enthusiasm for the local use of the sulfonamides in chronic sinus infection has not been borne out by later reports, and there have been studies indicating that a 5 per cent sodium sulfathiazole solution is deleterious to the mucous membranes. At this point I would like to cite the case of the following patient who came under my care last summer, and which would seem to indicate that there is a place for penicillin in the treatment of some cases of chronic sinusitis. The local treatments in this patient were carried out by Dr. Stuart Craig.

The patient, Mrs. C., aged 60, had had chronic purulent pansinusitis for many years, accompanied by severe headaches which could be partially relieved by irrigations. The washings invariably yielded a

considerable amount of thick yellow pus which showed a pure growth of hemolytic *Staphylococcus aureus*. For the past year or two the patient had had considerable pain in the joints and muscles which possibly resulted from the chronic sinus infection.

On July 19th the patient was started on intramuscular injections of penicillin, 10,000 units every three hours, except for a midnight injection which was 15,000 units. The 3 00 A.M. injection was omitted. A total of 75,000 units of penicillin was administered each 24 hours, and this was continued for 14 days to a total of 1,000,000 units by the intramuscular route. Simultaneously the patient's sinuses received daily irrigation with penicillin in normal saline, 250 units of penicillin to each cc of saline. In addition to the daily washing, the nose and throat were sprayed every two hours with a penicillin solution of similar strength. It was found that stronger solutions of 500 units to the cc caused some irritation to the nasal passages, so they were discontinued.

After 14 days of this treatment the nasal mucosa was much less congested, the amount of secretion gradually diminished, and the character of the discharge had changed from a purulent to a mucoid character. Suction of the nasal passages brought down only a small amount of the material compared with the former large quantity. At the conclusion of two weeks, intramuscular injections were discontinued, but the nasal spray was kept up, the sinuses being washed out two to three times a week.

Three weeks later the headaches had practically disappeared and the mucous membrane presented a healthy pink appearance. A moderate amount of mucus was still discharged, however, from the sinuses.

On September 15th, two months after the institution of penicillin treatment, the mucous membrane still maintained its healthy appearance. The nasal mucosa was much less congested than on last note. There was a small retention still in the upper ethmoid of mucopurulent discharge. No headaches or pain in the sinuses or cranium.

OTITIS MEDIA AND MASTOIDITIS

Otolaryngologists are in greater accord on the value of the sulfonamides in acute otitis media. Bowers⁸ states that the necessity for mastoidectomy is reduced 50 per cent by the prompt use of the sulfonamides for otitis media, and this view is shared by many other laryngologists and internists as well.

BRONCHITIS

Acute and subacute bronchitis are common complications of coryza and influenza, and it is the opinion of the writer, based on considerable experience, that the severity and duration of acute bronchitis can often be mitigated by the use of sulfonamide therapy. Naturally this depends a great deal on the bacterial agent responsible for the bronchitis.

So far I have said very little about the use of penicillin for the very good reason that in acute upper respiratory infections my experience with the drug has been very limited. That of course has been the case with most civilian physicians. However, in some of the larger clinics penicillin has already been used experimentally in the treatment of these infections.

Because of the difference of opinion which exists as to the value of sulfonamides in acute upper respiratory infections and because of my limited experience with penicillin, I recently sent out a short questionnaire to twelve of my colleagues who have been particularly interested in the use of sulfonamides and penicillin in acute upper respiratory infections. Six were internists and six were otolaryngologists. All of these men were physicians who have had unusual opportunity to study these drugs in large metropolitan clinics. The responses were interesting and rather surprisingly consistent.

The first question was "Do you advocate the use of sulfonamides in the treatment of uncomplicated coryza and influenza?" Eight of the 12 physicians gave an unqualified "No" to this question. Four otolaryngologists advocated the use of sulfonamides both locally and orally in severe infections with the aim of preventing complications. For local use, four of the otolaryngologists recommended Pickrell's solution, 2.5 per cent solution of sulfadiazine in 8 per cent triethanolamine solution.

2. Do you favor the use of sulfonamides in the treatment of acute sinusitis?

The response of all twelve to this question was "Yes", and 11 agreed that the drug was beneficial in shortening the course of the infection. One otolaryngologist expressed some doubt.

V. B. Hirst writes "I have used the sulfonamide drugs locally in the treatment of sinuses with excellent results. The treatment has been with irrigation. In the past two or three years we have shortened the course of these cases very much, even the very foul types, and I am

sure have prevented a lot of surgery ”

John Kernan writes “At times the sulfonamides seem to work magic, especially on acute sinuses. However, much more careful checking should be done with cultures in order to select the proper drug to combat the particular organism involved in the case ”

3 Do you favor the use of sulfonamides in *chronic* sinus infections, especially those of *Staphylococcus aureus* origin?

There was very little enthusiasm expressed by either the internists or the otolaryngologists for sulfa therapy in this condition. Practically all agreed that the results were very disappointing, and this was true whether the drug was used orally, as it was by the internists, or locally by the otolaryngologists.

4 Has oral administration of sulfonamides any advantage over the local use of the drug?

Four internists and four otolaryngologists preferred oral administration, four otolaryngologists employed both methods.

Walsh McDermott believes that oral administration has definite advantages. As he expresses it: “Sulfonamide is not an antiseptic solution, so must be taken up by the bacteria deep in the lesion. It seems to me the only way this could occur consistently would be if the blood supply of the infected lesion carried sufficient quantity of the drug. In addition, there is a strong suspicion, but no unequivocal proof, that local use of sulfonamides leads to increase of sensitization to the drug ”

5 Do you advise sulfonamides as routine in the treatment of acute otitis media?

All answered “Yes”, except one otolaryngologist who voted “No” because in his opinion they masked the onset of mastoiditis. The 11 who voted “Yes” were all convinced that the oral, or both oral and local use of sulfadiazine markedly reduced the incidence of mastoiditis and other ear complications.

Frank Horsfall writes: “Acute otitis media seems to me to be definitely improved, sometimes markedly so, by the use of sulfonamides in full therapeutic doses ”

6 Will penicillin treatment shorten a cold?

Three answered “No”. Four were in doubt. Five had had no experience with penicillin in the treatment of common colds.

7 Is penicillin of value in the treatment of acute sinusitis and acute otitis media?

Six physicians (four internists and two otolaryngologists) replied "Yes", one said "No"

Francis Blake writes "Penicillin will cure many cases of otitis that have failed to respond satisfactorily to sulfonamides. We have treated about 40 cases, the majority being due to *Streptococcus hemolyticus*, many with mastoiditis, some with beginning meningitis. The response has been almost perfect in hemolytic streptococcus infections, and very good in staphylococcus and pneumococcus infections. Penicillin was of no value in *Hemophilus influenzae* infections"

8 What success have you had with penicillin in the treatment of chronic sinusitis?

Two internists and one otolaryngologist replied "Good". Two otolaryngologists answered "Poor". One gave a qualified answer.

9 Have you used penicillin locally or parenterally for these infections?

Five internists had used the drug only by the parenteral route. One both parenterally and locally. The otolaryngologists have usually employed penicillin by both methods, though one had used it only locally. The dilution of penicillin for local use varied considerably, all the way from 100 units to 2000 units per cc of saline solution. The tendency, however, was toward the weaker dilutions.

Stuart Craig writes "The local use of sulfonamides, except in selected cases, is not outstandingly effective. The administration of even heavy doses for chronic cases with degenerative changes and thickened membranes has not proved effective in our hands. From the limited opportunity we have had to use penicillin locally in the sinuses, I would believe that it offers great promise when it can be used for the treatment of both acute and chronic sinusitis with no restrictions as to the amount available."

10 Have you seen allergic reactions, such as fever and drug rashes from the local use of sulfonamides?

Four internists answered "No". One had seen a few allergic reactions. It was interesting that 4 out of the 6 otolaryngologists replied "Yes" to this question, suggesting that reactions were more likely to occur from local than from oral use of the drugs.

Wesley Bowers writes "It seems that we shall always have to bear in mind that using sulfa drugs for trifling conditions may render the patient sensitive to them, so that when they are badly needed for

meningitis or pneumonia, the patient would be forced to go without them"

Walsh McDermott writes "I have seen allergic reactions in patients receiving sulfonamides by mouth who gave a history of previous use of the drug locally"

12 Have you seen allergic reactions following the use of penicillin?

Three internists replied "Yes", three "No" The otolaryngologists all replied "No"

McDermott says "Febrile spikes as high as 40° C have occurred following intramuscular injections of penicillin in previously afebrile patients I have also seen two patients with definite serum sicknesslike syndrome following penicillin therapy, characterized by urticaria, periorbital edema, myositis, arthralgia and fever"

Summarizing the questionnaire, we can make the following fairly consistent generalizations

1 There is little or no enthusiasm for the use of sulfonamide drugs for the treatment of the common cold and influenza A few otolaryngologists recommend the drug to prevent complications, but they are in the minority

2 Both internists and otolaryngologists are enthusiastic over the use of sulfonamide therapy in acute sinusitis They are much less enthusiastic concerning such treatment in chronic sinusitis

3 Practically all are agreed that sulfonamides are valuable in the treatment of acute otitis media as a means of preventing mastoiditis

4 There is no enthusiasm for the use of penicillin for the treatment of the common cold, but there is almost complete uniformity of opinion that penicillin is of value in the treatment of acute sinusitis and acute otitis media.

5 There is only moderate enthusiasm for penicillin therapy in chronic sinusitis

6 All are agreed that successful therapy with either sulfonamides or penicillin is in large measure dependent upon the type of bacteria responsible for the infection

7 Allergic manifestations are occasionally seen with both sulfonamides and penicillin, usually in the form of an urticarial rash

8 Oral administration of sulfonamides and parenteral injection of penicillin are favored over local application of these agents Combined systemic and local treatment is also popular with both groups

COMMENT

One fact seems to stand out clearly as a result of this discussion. There is no indication for the administration of either sulfonamides or penicillin in the treatment of ordinary coryza or grippe. As McDermott says "With the ordinary cold I see no point in taking the risk of sulfonamides or the *discomfort* of penicillin."

In certain selected cases where the patient knows from past experience that his cold will probably be followed by some complication, one might be justified in using either sulfadiazine or penicillin, but even in these cases there is often some doubt as to the desirability of the procedure.

There is something quite Utopian about the eagerness with which both the medical profession and the laity search for a cold cure, yet when all is said and done, in the vast majority of cases, the common cold is a trivial infection. It makes us uncomfortable for a few days, but usually (with the help of aspirin, atomizers and Scotch whiskey!) we keep at our routine duties. There is a group of patients, of course, for whom the common cold is a much more serious problem. They know from past experience that complications in the sinuses or trachea are going to follow. In a good many children the middle ear has a rather terrifying way of lighting up with every coryza. It is in this group of patients that chemotherapy has its important field. The writer's own experience and that of the physicians whom he has consulted in this questionnaire indicate that sulfonamides and penicillin both have a place in the treatment of these complications. As we obtain more experience penicillin may prove to be the preferable agent. In fact it may entirely replace the sulfonamides.

I don't believe that chemotherapy would be generally successful in any sinus infection that was not at the same time receiving adequate surgical drainage. With drainage, chemotherapy, either sulfadiazine or penicillin, should be effective in properly selected cases. A good deal more investigation will have to be done before dogmatic answers can be arrived at. In the meanwhile it would seem the wiser course for the practitioner to limit his use of these agents to the treatment of sinusitis, otitis, bronchitis and the other less prevalent complications of acute upper respiratory infections.

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BULLETIN OF
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JUNE 1945

MASS SULFADIAZINE PROPHYLAXIS
OF RESPIRATORY DISORDERS IN
THE U S NAVY*

ALVIN F COBLURN

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INTRODUCTION

THE delicate balance which exists between respiratory pathogens and the human host is frequently disturbed in times of war. A balance unfavorable to military personnel is produced in at least three ways: (a) by the spreading of virus infections of the respiratory tract, (b) by the introduction of bacterial strains with great pathogenicity, and (c) by the dissemination of these strains among susceptible recruits. This sequence occurred in World War I. Outbreaks of measles were common at training camps and influenza reached pandemic proportions. Following these virus diseases, hemolytic streptococcus acquired great pathogenicity. In 1918-19 this bacterium accounted for at least 242,000 casualties (exclusive of pneumonia and probable streptococcal diseases) in the armed forces. Approximately 7 per cent of the mean annual strength of the armed forces was hospitalized with streptococcal infections, approximately 56,000 men were crippled with rheumatic fever or acute rheumatism, the mortality rate from streptococcal infection

was high. It is now well known that deaths from respiratory pathogens during World War I exceeded the fatalities of trench warfare.

At the onset of World War II, military medicine had equipped itself to prevent fatalities from respiratory infections. Nevertheless, hemolytic streptococcus accounted for over 47,000 infections in the U S Navy during the first year of the war. Most of these were minor casualties, however, there was an impressive list of disabling streptococcal complications: 5,231 otitis, 2,736 sinusitis, 1,002 acute arthritis, 869 rheumatic fever, 876 valvular heart disease, and 171 mastoiditis. The low mortality rate associated with the advent of sulfonamides obscured the fact that at least 2,700,000 man-days were lost to the Navy during the first year of World War II from proved or probable streptococcal infections. Nevertheless, in 1943 the morbidity rate from scarlet fever reached a level far higher than ever recorded in the history of the U S Navy.

It was anticipated that a marked increase in the incidence and severity of streptococcal infections would occur in the U S Navy during 1943 because conditions occasioned by rapidly expanded training programs were comparable to those created in experimental epidemiology. It was believed that under existing conditions in training camps, hemolytic streptococcus would manifest increased infectivity, would develop variants endowed with great pathogenicity and would create incalculable damage to Navy personnel. This sequence of events became manifest in 1943. During the summer months of 1943 the activity of meningococcus and pneumococcus subsided. However, at one Naval activity hemolytic streptococcus maintained its pathogenicity and late in 1943 this bacterium exhibited increased virulence. Furthermore, strains of this bacterium, identified serologically as types 17, 1, and 19, maintained their pathogenicity when transplanted by carriers to other geographical environments and even initiated streptococcal epidemics at Naval activities situated in southern states.

FACTORS IN THE PATHOGENESIS OF RESPIRATORY EPIDEMICS AT NAVAL TRAINING STATIONS

Five conditions favoring the development of respiratory epidemics were satisfied at several large Naval training stations in World War II. Fresh, highly susceptible recruits were introduced almost daily, there was a high rate of change in population during the program for rapid

training, overcrowding and the congestion of large numbers of men in sleeping quarters occurred, outbreaks of influenza or measles developed at large training centers, most of the training stations were seeded with strains of respiratory pathogens that manifested great communicability.

Other less obvious factors, which varied from station to station, were also operative. At some, temperatures were high indoors and extremely low outdoors during the winter months. At others, dust storms presented a serious local problem during the summer months. Rapid fluctuations in outdoor temperatures, rain, snow, fog, and other climatic states were variables at each activity. Many of these conditions, not subject to appraisal, were unfavorable to the normal, physiological responses of the host and, therefore, favorable to the invasion of bacterial respiratory pathogens.

Conditions which facilitate the transmission of respiratory pathogens during recruit training are now being recognized. (1) The contamination of food, which may cause explosive outbreaks of throat infections, is always a potential danger. (2) The direct transmission of respiratory pathogens from infected individuals during the incubation and convalescent states is accelerated by overcrowding and billeting in times of war. The use of double-deck bunks permits the direct transmission of large inocula of bacteria from man to man. (3) The possibility of insufflation of infected particulate matter occurs with intensive recruit training in swimming. One man plunges into the water of a pool and contaminates it with purulent exudate from the nasal sinuses or the respiratory tract. This material, uninfluenced by short exposure to chlorine, may be forced under pressure into the ears, sinuses or respiratory passages of the recruits who follow in quick succession. The chlorination of swimming pool water may give little protection under these conditions although affording a satisfactory bacterial count on analysis. Furthermore, chlorine acts as an irritant to the mucous membranes of many individuals. This may be one of the several factors inherent in swimming which lower the resistance of mucous membranes and increase susceptibility to the invasion of bacterial pathogens already harbored. (4) Indirect transmission of airborne respiratory pathogens is tremendously accelerated by rapidly expanding training programs. Convalescent carriers of hemolytic streptococcus are per force barricked in recruit camps and contaminate decks and blinkers. These barricks are filled with new trainees as

soon as billets become empty. Dust and blanket lint containing millions of organisms are disseminated with each cleaning of the decks and manipulation of blankets. The rapid turnover of recruits and the failure to recognize the importance of dust control measures permit ideal conditions for the inhalation of small numbers of respiratory pathogens by large numbers of trainees. If these trainees be recruits, their susceptibility is further enhanced by a coincident lowering of resistance associated with acclimatization, changes in living conditions, and reactions to active immunization against tetanus, smallpox, yellow fever, typhus fever, and enteric infections (5). The indirect transmission of air-borne respiratory bacterial pathogens is further accelerated by the passage, directly or indirectly, of certain viruses. Measles and influenza are air-borne infections disseminated with great facility in crowded barracks. Irrespective of whether an individual recruit contracts or escapes these virus infections, there can be no doubt that one of the final effects of virus activity in a Naval training station is increased pathogenicity of the prevalent strains of hemolytic streptococcus. With increased pathogenicity of this bacterium, the morbidity rate rises. This rise is followed by increasing dissemination, which facilitates the epidemic process.

Theoretically, it is possible to break this process of spreading contagion because methods are available to control each factor in the initiation and perpetuation of a respiratory epidemic. Medical science has almost eliminated the explosive outbreaks caused by the ingestion of food infected with hemolytic streptococcus. Careful screening of convalescents before their return to duty and elimination of double-deck bunks will reduce the incidence of "return cases" who have been infected directly by the inhalation of infected droplets. The institution of technique for dust control, such as oiling of the blankets and decks with bactericidal emulsions, will reduce the incidence of indirectly transmitted air-borne infections. The cessation of instruction in swimming pools will eliminate infections caused by insufflation. The suppression of influenza by active immunization and measles by passive immunization may remove the most important virus factors. The protection of a recruit from infection during the first three weeks of "boor" training, when he is being acclimatized and actively immunized, will increase his resistance at the time of maximum exposure to hemolytic streptococcus.

Practically, it is impossible to control all of these factors while conducting a rapidly expanding training program. The future will undoubtedly see Preventive Medicine apply the necessary control measures. The present must accept the fact that the dissemination and inhalation of air-borne respiratory pathogens is not yet controlled by Naval sanitation. The medical officer cannot yet prevent the seeding of microorganisms, the rooting of these pathogens in the floor dust, the growth of these infectious agents among his men, the branching of this epidemic process to other men in his barracks, but he can now check the fruition of an epidemic process by preventing implantation of respiratory pathogens in susceptible recruits. It was for this purpose that the heroic measure of mass chemoprophylaxis was employed by the U S Navy.

A PROGRAM FOR THE CONTROL OF STREPTOCOCCAL INFECTIONS

The Navy's enormous loss of man-days to *Streptococcus haemolyticus* was only one of the compelling reasons for instituting a Streptococcal Control Program. For military and civilian welfare it became essential to prevent the dissemination of respiratory pathogens among Naval personnel, to prevent the induction of rheumatic fever with the development of incapacitating heart disease, to prevent the invasion of streptococcus into deep tissues with the formation of suppurative lesions and to prevent the spreading of this highly virulent organism from one Naval activity to another. To attain these objectives, a long-term Streptococcal Control Program was instituted in November 1943.

The first objective of this program was to check the rapidly rising respiratory infection morbidity rates in the winter of 1944 by preventing the implantation of pathogenic bacteria in the nasopharynx. Continuous chemoprophylaxis was selected as the most promising control measure. To test the applicability of chemoprophylaxis under controlled conditions and to determine a standard prophylactic dose of sulfadiazine, programs were designed for five large northern training stations with high respiratory disease rates. Groups of trainees were then selected to receive sulfadiazine prophylaxis and comparable groups to serve as untreated controls. At each station these groups were placed under the supervision of an Epidemiology Unit.

On December 1, 1943 this controlled program was initiated at five training stations. Data on the incidence of respiratory infections in the

"treated" and control groups were collected for three months. With the accumulation of these data, the effectiveness of mass prophylaxis was manifest. It was then decided to extend the program to three other Naval activities experiencing a high incidence of streptococcal infections and to discontinue the use of untreated controls in the five Naval activities at which the sulfadiazine program was already in operation. Continuous mass prophylaxis was accordingly extended to about fifty camps of eight Naval activities, and this program was continued throughout the spring months of 1944.

ADMINISTRATION

Camps with high streptococcal morbidity rates, or half of each of these camps, were selected as the groups to receive chemoprophylaxis. Similar camps, or the other half of a camp, served as controls. Accurate daily records were kept of all patients with respiratory diseases seen at sick call or admitted to dispensary sick bay or hospital. In addition, an epidemiologist made daily visits to each recruit unit dispensary and to the Naval hospital. Clinical diagnoses on all respiratory diseases were checked and corrected. Throat cultures were made on all patients with frank or probable streptococcal diseases, including scarlet fever, tonsillitis, pharyngitis, erysipelas, otitis media, mastoiditis and sinusitis.

Blood samples were obtained for the determination of blood sulfadiazine levels from cases with frank or probable streptococcal or meningococcal diseases in the treated areas. Beta hemolytic streptococci recovered from the throat flora were isolated in pure culture, transferred to blood agar slants and shipped to the Streptococcus Typing Laboratory at the National Naval Medical Center, Bethesda, Maryland, for grouping, typing, and sulfonamide-fastness studies.

Clinical records were begun several weeks prior to the institution of prophylaxis to establish a preliminary base line. The dispensing of sulfadiazine tablets was placed under the direct personal supervision of the company commander and company clerk of each company. A "check-off list" insured that each man received his dose, and he was required to swallow this 1 gram with water in the presence of the company commander. No one was excused from taking the drug unless possessing a certificate from the medical officer of his unit indicating that he was sensitive to sulfonamide.

RESULTS

The effectiveness of chemoprophylaxis in the control of streptococcal respiratory infections became apparent at the end of the first week. After two weeks, the incidence of rheumatic fever began to decline and then fell progressively. By the end of one month the incidence of scarlet fever, tonsillitis, and rheumatic fever reached a relatively low level in each group receiving chemoprophylaxis. It was also apparent early in this program that sulfadiazine prophylaxis had no effect on the incidence of influenza, measles, atypical pneumonia and other diseases believed to be caused by filtrable viruses.

A. EFFECTIVENESS OF CHEMOPROPHYLAXIS IN THE CONTROL OF RESPIRATORY DISEASES

Continuous chemoprophylaxis with 1 gram of sulfadiazine daily was highly effective in preventing bacterial infections of the respiratory tract of susceptible recruits. This was evidenced in the following ways:

- 1 *Effect on Throat Flora* Throat culture studies were made on recruits upon arrival at a Naval training station and four weeks later. It was observed that men who did not receive chemoprophylaxis acquired hemolytic streptococcus in their throat flora. The carrier rate rose throughout training in control groups. However, in groups receiving chemoprophylaxis the carrier rate of hemolytic streptococcus either remained at the level observed on arrival or fell to a moderately lower level. This is illustrated in Chart 1.

- 2 *Effect on Total Respiratory Infection* The incidence of respiratory infections was lower in all groups receiving chemoprophylaxis than in the controls. This difference in morbidity rates was due largely to the effectiveness of sulfadiazine in preventing streptococcal infections. This is illustrated by observations made at a Naval training center where measles and influenza (catarrhal fever) were prevalent and bacterial respiratory pathogens disseminated throughout all areas of this training activity. Chart 2 shows the effectiveness of chemoprophylaxis under conditions least favorable to the host and most favorable to the spread of respiratory infections.

- 3 *Effect on the Incidence of Respiratory Symptoms* Men in groups receiving chemoprophylaxis had fewer respiratory symptoms than men in control groups. At some stations the reduction in sick call

EFFECT OF SULFADIAZINE IN PREVENTING IMPLANTATION OF HEMOLYTIC STREPTOCOCCUS IN THE THROAT FLORA OF RECRUITS

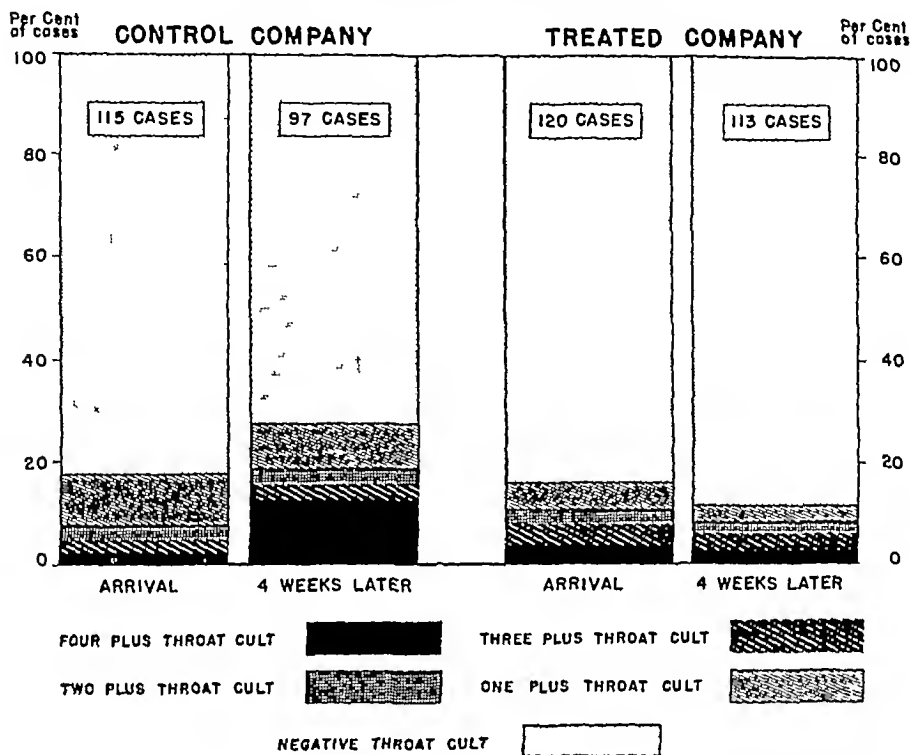


Chart 1 Throat culture findings in recruits on arrival and four weeks later

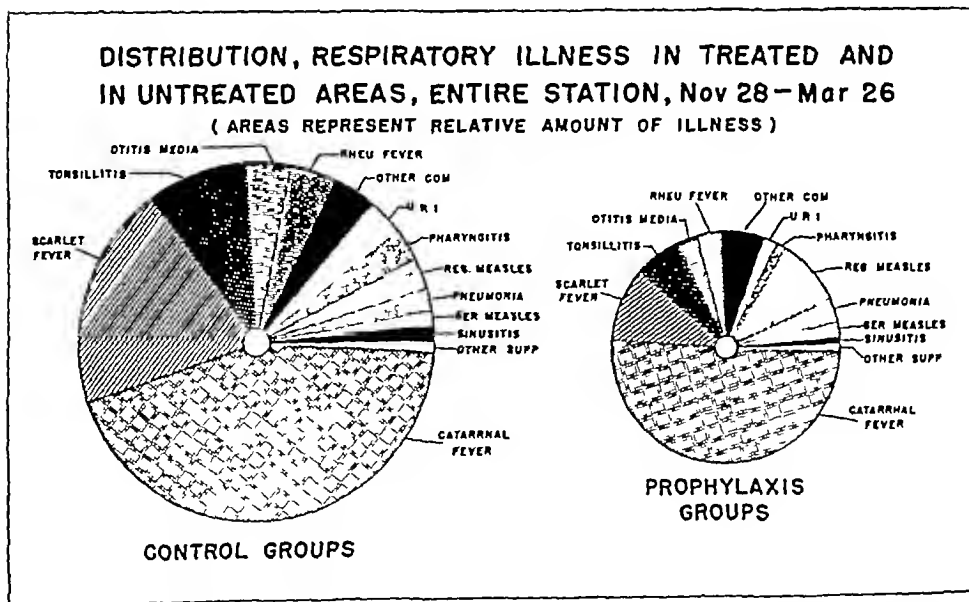


Chart 2 Respiratory diseases on a station of 50,000 men, about half of whom received chemoprophylaxis

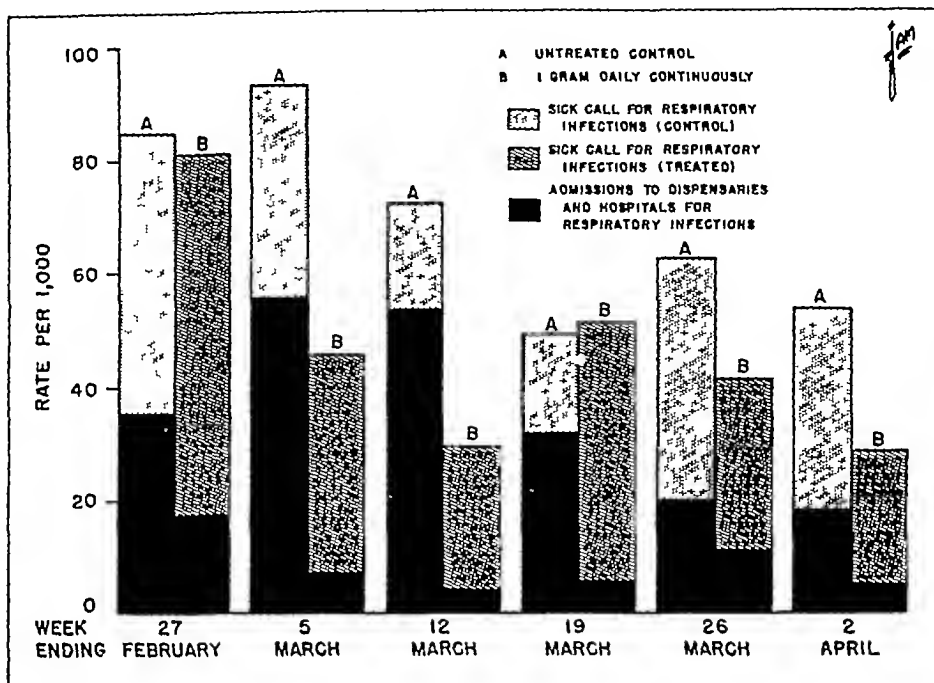


Chart 3 Sick call and admission rates for respiratory symptoms in a camp of 5,000 men, half of whom received chemoprophylaxis

visits for respiratory symptoms was 50 per cent in groups receiving chemoprophylaxis. At other stations the reduction was less striking. This variation was probably associated with the relative prevalence of virus diseases. Observations presented in Chart 3 indicate what may be expected from chemoprophylaxis during the winter months when both virus and bacterial respiratory pathogens are active in a camp of 5,000 men.

4 *Effect on the Incidence of Severe Respiratory Diseases* One of the most striking effects of chemoprophylaxis has been the prevention of respiratory diseases which require hospital care. This was indicated in Chart 3 and is more striking in Chart 4. Chart 4 shows the admission rates to a Naval hospital from a training center where 15,000 recruits received chemoprophylaxis and 10,000 recruits were observed as controls.

5 *Effect on the Sequelae of Influenza* Although chemoprophylaxis does not lower the incidence of influenza, morbidity rates for respiratory infections following influenza were lower in groups receiving sulfadiazine than in control groups. This is illustrated in Chart 5. This

ALL TRANSFERS TO HOSPITAL FOR UPPER RESPIRATORY INFECTIONS

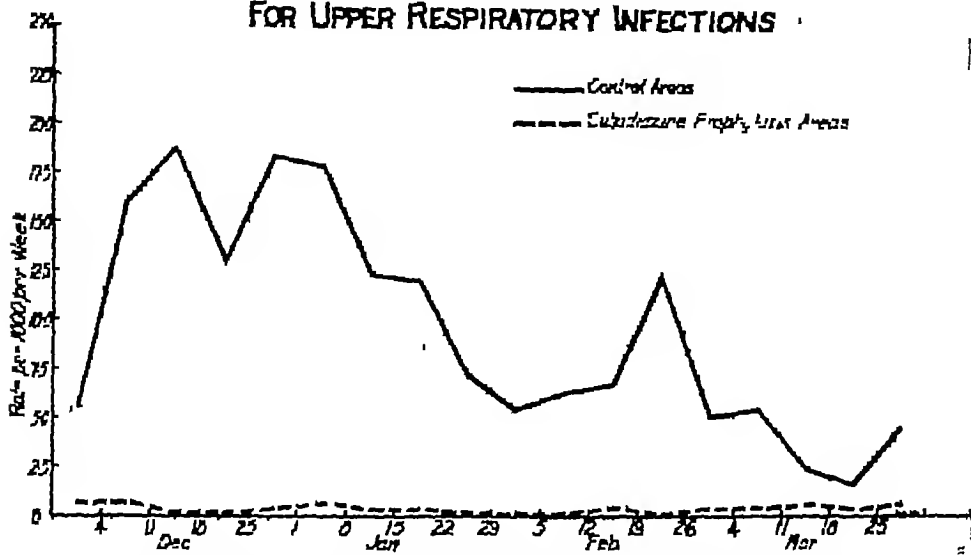


Chart 4 Hospital admission for upper respiratory diseases on a station where 15,000 recruits received chemoprophylaxis and 10,000 recruits served as untreated controls

chart shows the morbidity rates in two battalions at one camp Both experienced a severe outbreak of influenza in November 1943 Following this outbreak, the incidence of respiratory infections was significantly lower in the group receiving prophylaxis than in the control group

B EFFECTIVENESS OF CHEMOPROPHYLAXIS IN THREE BACTERIAL INFECTIONS

It has been pointed out that the effectiveness of chemoprophylaxis in the respiratory tract is limited to bacterial infections The effectiveness of sulfadiazine in preventing these bacterial diseases is, moreover, determined by the susceptibility of the causative agent to concentrations of 0.5 to 1.0 mgm per cent of sulfadiazine on the mucous membranes of the respiratory tract Meningococcus was found most susceptible, hemolytic streptococcus, in most instances, proved highly susceptible There was great variation in the susceptibility of pneumococcus

1 *Effect on Cerebrospinal Fever* This disease was eliminated by chemoprophylaxis Chart 6 illustrates the effect of the administration

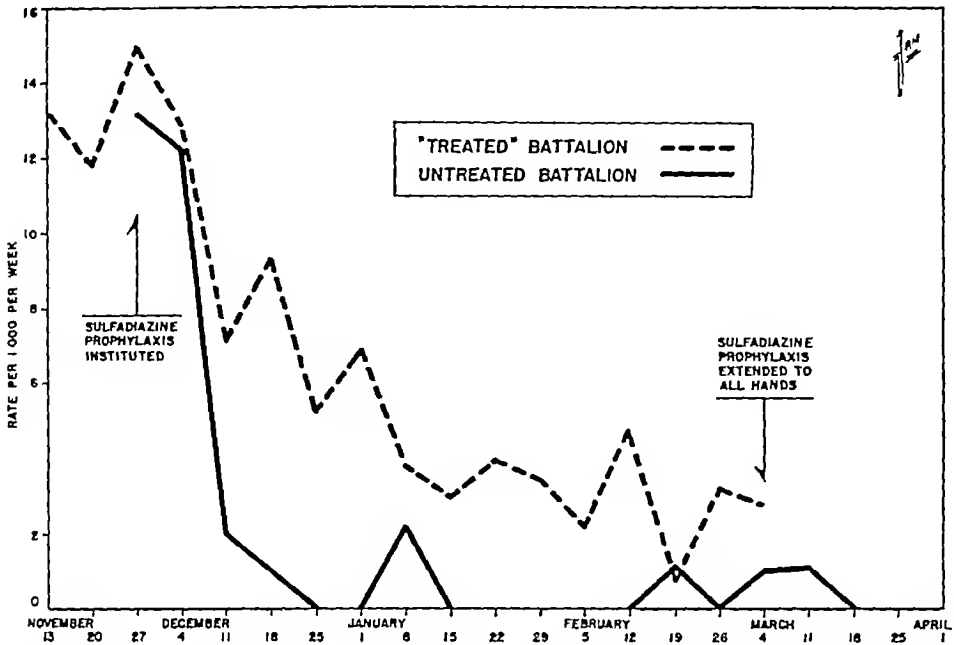


Chart 5 Morbidity rates for respiratory diseases during and following an outbreak of influenza in two battalions of 1,000 men each

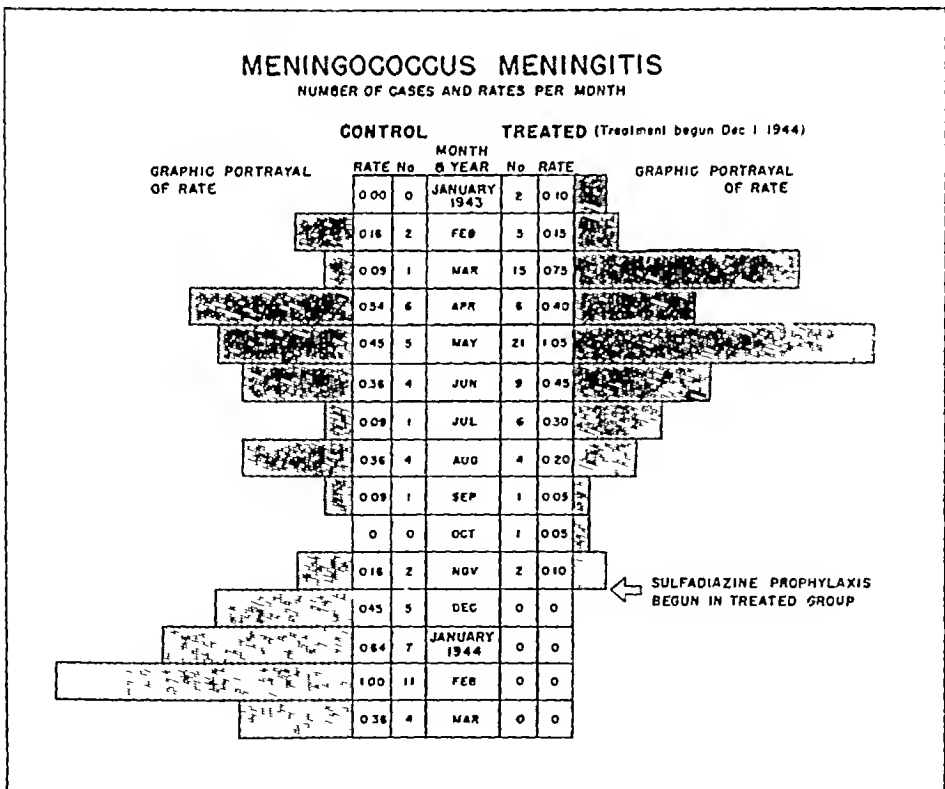


Chart 6 The incidence of meningococcus meningitis on a large training station Chemoprophylaxis was instituted on 1 December 1943 in 30,000 recruits

EFFECTIVENESS OF PROPHYLAXIS DURING EPIDEMIC PROCESS

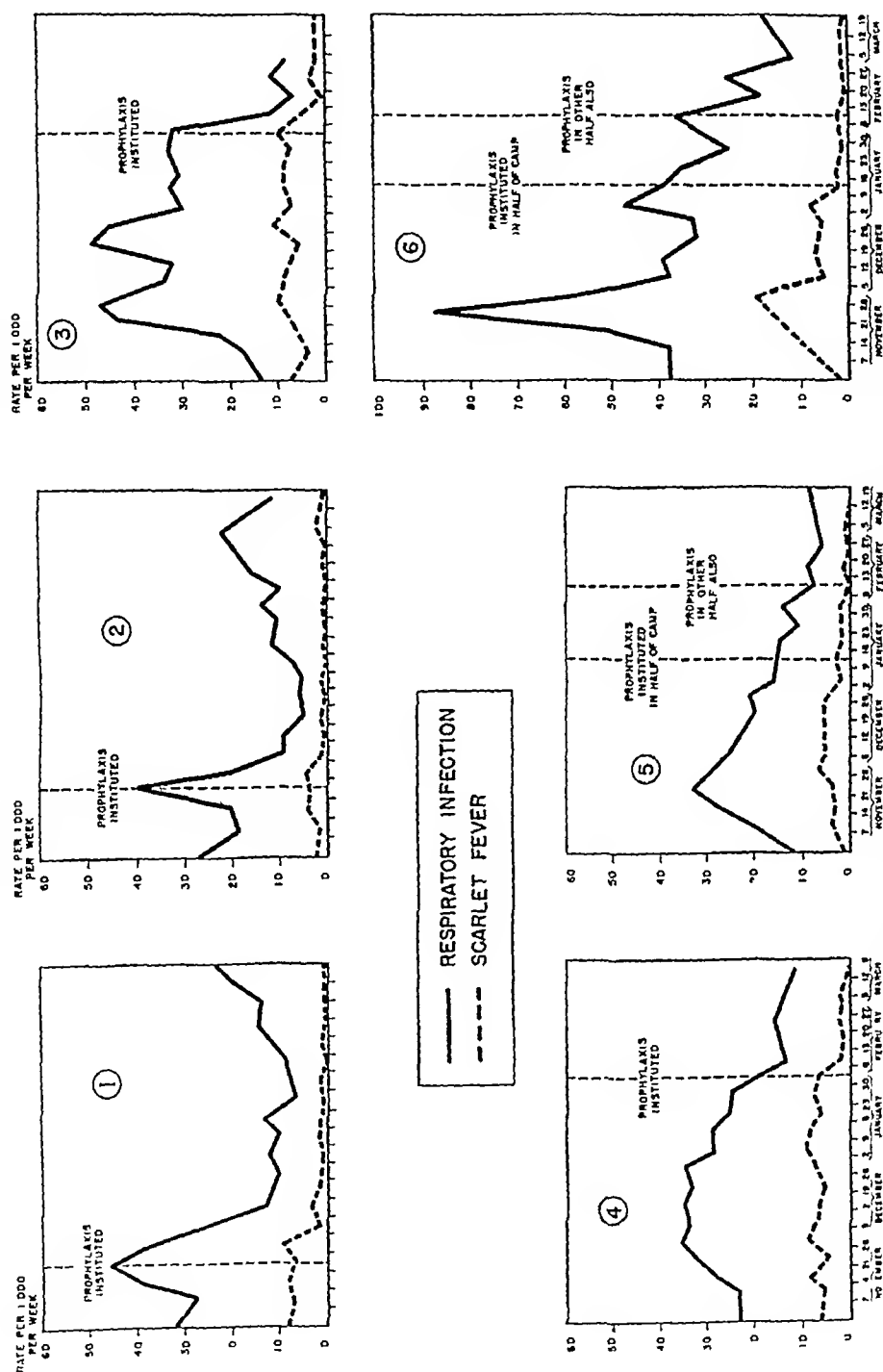


Chart 7 Morbidity rates for scarlet fever and respiratory infections before and following chemoprophylaxis in camps of 5,000 men

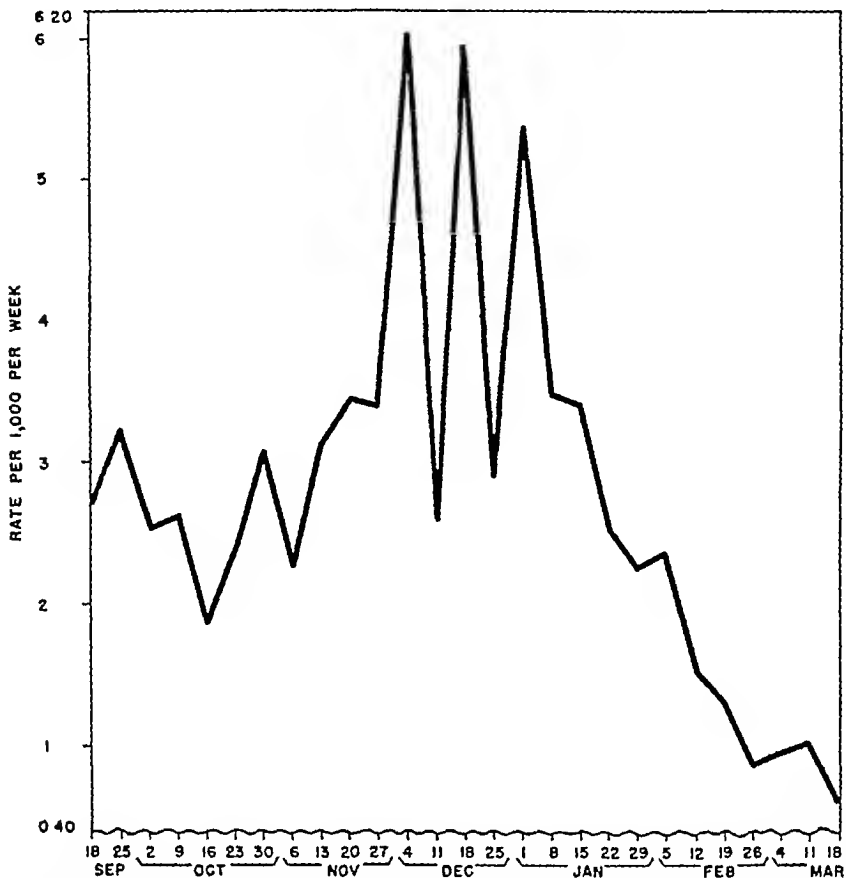


Chart 8 Morbidity rates for scarlet fever among 50,000 men Chemoprophylaxis was instituted among 10,000 men in December 1943 and extended to 30,000 men in January 1944

of sulfadiazine, 10 gram daily, in a camp where 30,000 recruits received prophylaxis and 30,000 recruits were observed as controls

2 *Effect on Scarlet Fever* Chemoprophylaxis was highly effective in preventing scarlet fever. At one training center, where 15,000 recruits received prophylaxis for three months and 25,000 for three subsequent months, scarlet fever was eliminated in groups receiving prophylaxis. This training center was situated in New York State and had previously experienced high morbidity rates for scarlet fever.

The institution of sulfadiazine prophylaxis at camps where scarlet fever was already epidemic was also found highly effective. Irrespective of whether the epidemic was in an early stage, at its height, or subsiding, chemoprophylaxis almost eliminated scarlet fever. The most

severe test given sulfadiazine during this program was at a Naval Training Center in northern Idaho. Both virus and bacterial respiratory pathogens were widely disseminated throughout this activity. The institution of chemoprophylaxis in each camp was followed by a prompt reduction in the incidence of scarlet fever. This is shown in Chart 7. The extension of sulfadiazine prophylaxis to the entire activity was followed by a reduction in the morbidity rate from 6 to 0.6 per 1,000 per week. This is shown in Chart 8.

3 *Effect on Pneumonia* At some stations chemoprophylaxis lowered the incidence of pneumonia by 50 to 80 per cent. At other stations control measures were ineffective. This variation was associated chiefly with two factors: (a) the prevalence of atypical pneumonia and (b) the prevalence of drug-resistant strains of pneumococcus. At one activity in Oklahoma, most of the cases of pneumonia were atypical. At another activity in Idaho, the prevalent types of pneumococcus were found to be resistant to sulfadiazine concentrations of 2 mgm per cent but susceptible to therapeutic blood levels of sulfadiazine (over 5 mgm per cent). Sulfadiazine prophylaxis eliminated primary streptococcal pneumonia but failed to influence the pneumonia morbidity rate at this station while drug-resistant strains of pneumococcus were prevalent. This failure, shown in Chart 9, illustrates what may be expected if epidemic strains of hemolytic streptococcus or meningococcus are sulfonamide-resistant.

OBSERVATIONS ON DOSAGE AND SCHEDULE OF SULFADIAZINE ADMINISTRATION

Two daily dosages, 1.0 gram and 0.5 gram, were tested in this study. Companies were assigned odd or even numbers alternately at the Receiving Unit; the odd-numbered companies received one dosage, the even-numbered companies the other. A random distribution of such environmental influences as barracking, time in camp, messing, and other factors was assured. Careful physical examinations of patients with respiratory illnesses were made by the medical officers conducting the investigation, and throat cultures were obtained to determine whether these diseases were caused by bacterial agents.

The findings indicated that there was slightly more streptococcal illness among the group receiving 0.5 gram of sulfadiazine daily than among the group receiving 1.0 gram daily. In some camps, no statisti-

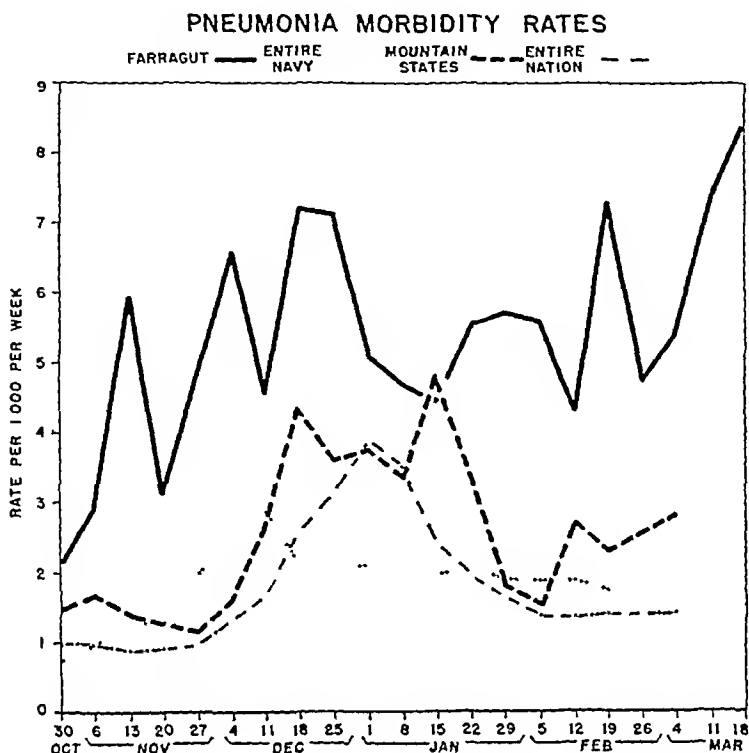


Chart 9 Morbidity rates for pneumonia The entire station received chemoprophylaxis in March 1944

cally significant difference in the effectiveness of the two drug dosages was demonstrable, other camps showed statistically significant differences. This variation may well have been due to the character of the prevalent strains of hemolytic streptococcus.

In addition to a continuous daily dosage, several schedules for administration were tested, such as, twice weekly, alternate weeks, alternate days. These schedules were found less effective and more difficult to administer than continuous daily prophylaxis.

POTENTIAL UNTOWARD EFFECTS OF CHEMIOPROPHYLAXIS

More than 600,000 men received sulfadiazine and there were approximately 3,000,000 man-weeks in this control program. Untoward effects anticipated include (1) a high incidence of drug reactions, (2) severe reactions terminating fatally, (3) sensitization of a large number of personnel, (4) initiation of sulfonamide-fastness among prevalent strains of hemolytic streptococcus. Each of the above points

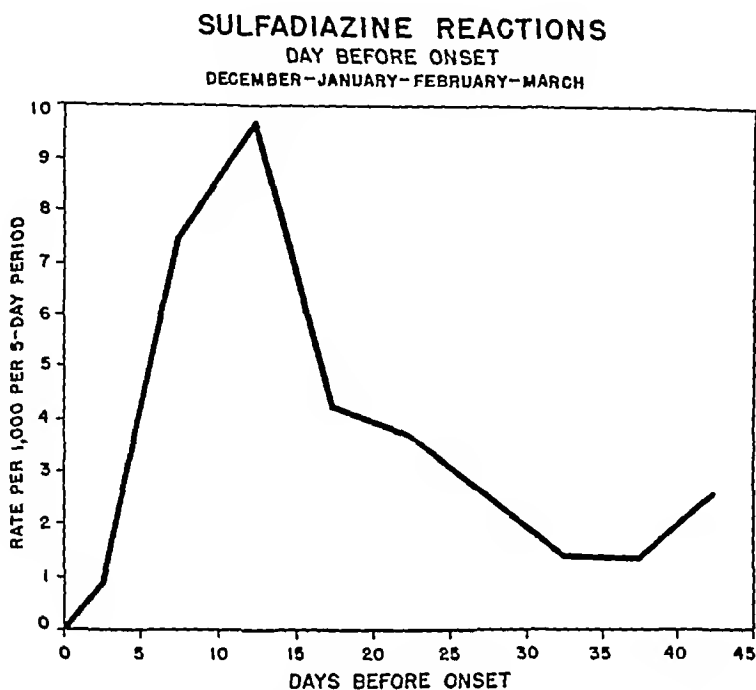


Chart 10 The distribution of sulfadiazine reactions in relation to duration of chemoprophylaxis

was carefully investigated, and the findings were as follows

1 The incidence of mild reactions was approximately 0.5 per cent. Nearly all of these reactions were dermal. Only half of the reactors were found sensitive to sulfadiazine on retesting with 10 gram of sulfadiazine. There were no renal complications from prophylaxis. Most of the reactions occurred during the first three weeks; there were a few immediate reactions among men who had previously received sulfonamide therapy; there were a few reactions as late as forty days after the institution of prophylaxis; the peak occurred between ten and fifteen days. This is shown in Chart 10.

2 Severe sulfonamide diseases occurred once in each 10,000 individuals, an incidence of 0.01 per cent. These were either exfoliative dermatitis or granulocytopenia. Altogether, thirty-nine men developed serious reactions. These reactions appeared to be reversible unless followed by sulfadiazine therapy. Fourteen deaths occurred among these 600,000 men from all causes, one from leukemia, two from granulocytopenia probably caused by prophylaxis, eleven from sulfonamide therapy administered to men with mild sulfadiazine reactions. There

were, also, two sulfonamide deaths in the control groups who received chemotherapy but no prophylaxis. After substituting the use of penicillin in place of sulfonamides for the treatment of these patients, there were no deaths among 350,000 men who received prophylaxis.

3 Sensitization did not appear to be produced by prophylaxis. The evidence for this is as follows:

a The subjects who manifested reactivity to sulfonamide prophylaxis after the first day gave no history of previous sulfonamide therapy. This indicates that they had not been sensitized in the past.

b Although about 5 per cent of human subjects develop reactions from sulfadiazine therapy, only 0.5 per cent developed reactions from sulfadiazine prophylaxis. This indicated that prophylaxis per se was not sensitizing.

c Continuing prophylaxis in several groups for as long as from three to six months did not increase the percentage of reactions. This indicates that prolonged prophylaxis did not sensitize.

d Stopping prophylaxis during alternate weeks or alternate months was followed by *no* increase in the incidence of reactions. Subjects who did not react to the first course of prophylaxis were not sensitive to subsequent courses. The administration of sulfadiazine therapy to men who had previously tolerated prophylaxis did not cause reactions. This is a further indication that prophylaxis had not sensitized.

4 Sulfonamide-fastness of prevalent strains of hemolytic streptococcus. Drug-fast strains of this bacterium were not detected clinically during this control program. It appeared that chemoprophylaxis does not favor the development of drug-fastness. The evidence for this is as follows:

a There was no general increase in the prevalence of any serologic type of hemolytic streptococcus in the groups on prophylaxis during the first five months of this program.*

b There was no increase in the proportion of hemolytic streptococci in the throat flora of individuals throughout the period of prophylaxis.

c There was no increase in streptococcal morbidity throughout the period of prophylaxis.

Sulfadiazine prophylaxis was, however, only 85 per cent effective

* During the sixth month of this program, type 19 became predominant at several Naval activities. Subsequent *in vitro* tests showed that strains of type 19 at one Naval activity were sulfadiazine resistant.

in preventing the implantation of hemolytic streptococcus. Some strains were able to infect individuals who had ingested 10 gram of sulfadiazine daily and who maintained a blood level of 2 mgm per cent. The explanation for this phenomenon is not yet known. It has been suggested that these individuals may have inhaled a heavy inoculum, may have been infected by direct contact, may have had a low concentration of sulfadiazine in the secretions of the respiratory tract, may have insufflated, during swimming instruction, purulent matter containing living microorganisms and cellular debris which acted as a sulfonamide inhibitor and afforded protection to the respiratory pathogen. These possibilities are real. However, another possibility which may be of much greater significance is the resistance of the microorganism to prophylactic doses of sulfadiazine.

That sulfonamide-fast strains were not prevalent during this program is shown by the fact that those individuals who contracted streptococcal respiratory tract infections while receiving prophylaxis responded satisfactorily to therapeutic doses of sulfadiazine. That sulfonamide resistance did not develop generally is shown by the fact that there was no increase in streptococcal morbidity throughout six months of prophylaxis. However, the typing results of May 1944 suggest that type 19 may have developed resistance to small concentrations of sulfadiazine. During this final month of the program, type 19 became the predominant organism at several Naval activities. At one activity where all hands received prophylaxis, the predominant type disappeared and type 19 was the causative agent in practically all respiratory infections.

Final solution of the problem of bacterial resistance to sulfadiazine has awaited the development of an "inhibitor free" medium which will support normal growth of all strains of Group A hemolytic streptococcus. Such a medium has recently been developed in the Typing Laboratory at Bethesda and appropriate studies are now being made to determine whether strains recovered after six months of prophylaxis are more resistant to sulfadiazine than strains recovered and frozen at the onset of this program. A final opinion will be forthcoming with the results of these cultural studies. At present, the possibility that some strains of Group A hemolytic streptococcus are resistant to 1 mgm per cent of sulfadiazine in the secretions of the respiratory tract seems real. This may well be the most important limiting factor of chemoprophylaxis in preventing implantation of Group A hemolytic streptococcus.

AN APPRAISAL OF MASS CHEMOPROPHYLAXIS

This report represents the observations and consensus of opinion of eight Navy epidemiology units. The data included come from the labors of hundreds of officers, petty officers and corpsmen. The material is obtained from large Naval training activities in all Naval districts of the United States where streptococcal infections are prevalent. The design of the prophylactic program was blueprinted to meet the needs of these stations with their individual respiratory disease problems. The execution of each program varied with the size, ability, imagination, and resourcefulness of the epidemiology unit. The serologic typing of hemolytic streptococcus was done under constant conditions in one laboratory. With this exception, each program encountered variables patently beyond control. Nevertheless, given one blueprint based on the fact that the presence of sulfadiazine molecules on the mucous membranes exerts a bacteriostatic effect on respiratory pathogens, given one-half million men to protect altogether, given one sulfonamide to administer, and given one objective, all these epidemiology units reported one conclusion. The strategy of mass chemoprophylaxis is fundamentally sound.

The degree of effectiveness of sulfadiazine prophylaxis is shown in these studies to be determined in part by the characteristics of the bacteria which the drug encountered. For example, the pathogenesis of a meningococcal infection seems to depend upon the spreading of this organism throughout a "herd," the pathogenesis of a streptococcal infection seems to depend upon implantation of a virulent strain in the susceptible host, the pathogenesis of pneumococcal pneumonia seems to depend upon the lowering of resistance of a carrier. The effectiveness of chemoprophylaxis in these diseases varies accordingly.

- 1 For example, it is known that so long as the carrier rate of meningococcus is kept low, cerebrospinal fever rarely develops. The presence of small amounts of sulfadiazine exerts such a highly bacteriostatic effect on meningococcus that the carrier rate is reduced to a minimum. Chemoprophylaxis has, therefore, proved to be a perfect protection against cerebrospinal fever in these one-half million men.

- 2 Previous studies have shown that sulfadiazine, either in prophylactic or therapeutic dosage, has little effect on the throat flora of carriers of hemolytic streptococcus. The present observations have proved

confirmatory. In addition, however, they have shown that the presence of small concentrations of sulfadiazine in the nasopharyngeal secretions will "screen out" hemolytic streptococcus. Implantation of this bacterium was prevented in most instances, irrespective of the pathogenicity of the prevalent strains. Only in a small percentage of instances did this microorganism penetrate the bacteriostatic effect of sulfadiazine. This occurred after the individual had been ingesting one gram of drug daily for a period of weeks and was maintaining a satisfactory blood level; this was observed in areas where the exposure to streptococcal infections was greatest and especially among recruits receiving swimming lessons, this was most striking at the time that the incidence of measles was high. Nevertheless, even under these conditions the presence of sulfadiazine in the nasopharyngeal secretions usually prevented the implantation of a new strain of hemolytic streptococcus. By this achievement chemoprophylaxis was at least 85 per cent effective in preventing streptococcal infections.

3. Previous studies have also shown that mechanisms essential for the pathogenesis of pneumonia are different from those of meningococcal and streptococcal infections. An individual may be a carrier of pneumococcus for many weeks and escape disease until an episode upsets the host-parasite balance in favor of the microorganism. The present observations show that a considerable percentage of the individuals developed pneumococcal lung infections and pneumococcal otitis media while maintaining a sulfadiazine blood level of about 2 mgm per cent. One factor in the pathogenesis of these diseases may have been indoor swimming. Another factor, demonstrated in certain instances, was the prevalence of a sulfonamide-resistant strain of pneumococci.

SUMMARY

Sulfadiazine prophylaxis has been administered to approximately 600,000 Naval personnel and approximately 300,000 similar personnel have been observed as controls.

The institution of this measure was followed by a marked reduction in the morbidity rates for respiratory diseases.

The incidence of respiratory symptoms observed at sick call was significantly lowered.

Hospital admissions for respiratory diseases were reduced from rates varying between 5 and 18 per 1,000 per month to less than 1 per 1,000 per month.

Meningococcal infections were eliminated

The incidence of pneumococcal pneumonia was significantly lowered at most Naval stations

Morbidity rates for respiratory diseases caused by filtrable viruses were unaffected

The most effective dosage tested was 10 gram daily

The administration of 0.5 gram of sulfadiazine daily was also found effective and was followed by fewer untoward reactions

Mild, untoward drug reactions were observed in about 0.5 per cent. Severe reactions occurred in 0.01 per cent of men taking 10 gram of sulfadiazine daily

Sensitization of Naval personnel to sulfonamides and the development of sulfadiazine-fast respiratory pathogens did not occur

This paper has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U S Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

The author is indebted for the data set forth in this paper to the following Epidemiology Units of the U S Navy:

Epidemiology Unit #12

Epidemiology Unit #13

Epidemiology Unit #19

Epidemiology Unit #22

Epidemiology Unit #42

Epidemiology Unit #43

Epidemiology Unit #67

Epidemiology Unit #89

DISTANT SECONDARY CIRCULATORY AND VASOMOTOR REACTIONS TO ACCIDENTAL ELECTRIC SHOCK*

GEORGE H HYSLOP

WHEN the electrical current traverses the body, its pathway is the shortest distance between entry and exit. What happens to tissues depends upon the amount of amperage and duration of the current.

Tissue reactions may be physiological or pathological. When the electric energy of the current is turned into heat, tissues may be burned and destroyed.

L. Alexander¹ states that 25 milliamperes or more may produce permanent damage to nerve tissues and blood vessels. A critical level for morphological alteration of nerve tissue is 30 milliamperes per 3 mm of nerve diameter for shocks of 5 seconds duration.²

One may define direct primary effects as limited to tissues traversed by the current. Indirect or secondary effects are those which occur in other tissues due to reaction originating in tissues traversed and directly affected by the current.

Prior to a few years ago, certain writers concluded that the blood vessels have less resistance to current than other tissues, or are especially vulnerable, thus allowing part of the current to traverse the body in a branching manner, and cause lesions in tissues supplied by these vessels.

This theory was probably devised to explain certain clinical phenomena, such as an immediate or delayed cerebral reaction to a current which passed perhaps from arm to arm, or from an arm to a leg, and traversed the trunk.

A. W. Weeks and L. Alexander³ demonstrated that the current chooses the shortest path from contact to contact without deflection by anatomical landmarks (thus indicating that the body acts as "a structureless gel"). They also demonstrated that in tissues adjacent to, but away from the current main path, the effective current conducted

* Read January 9 at the joint meeting of The Section of Neurology and Psychiatry and The New York Neurological Society.

rapidly decreases, that is, there is practically no diffusion of the current away or distant from its main path. Also, they demonstrated that when the current passes from a hind foot to a fore foot, the amounts traversing the aorta, vena cava, spinal cord and long back muscles were similar. As for blood vessels, it has been shown by F. Echlin⁴ that when the current traverses arteries, there is an initial constriction followed by a period of dilatation which may be severe and prolonged and cause secondary hemolysis of the blood in the veins. These reactions are limited to vessels traversed by the current.

However, in certain fatal cases, there may be widespread filling of blood vessels with non-clotted blood, called "hemogenized blood", which is regarded as a secondary effect of prolonged respiratory paralysis. Such respiratory paralysis may occur in individuals in whom the current has not traversed the respiratory center, but where there has been prolonged tetanic spasm of the muscles of the body, so that respiratory movements have been interrupted.

A number of authors have commented on the blood pressure responses to electric shock. I have not found in the literature any statistical evaluation of clinical material bearing on this point. It seems reasonable, however, to hold that if there is a systemic reaction to injury by the electrical current, then the blood pressure response would be similar to what occurs in systemic shock due to other causes. If the current directly affects the respiratory or circulatory centers in the medulla, or if it produces a definite effect upon either the heart muscle or the innervation of the heart, blood pressure reaction is to be expected with a drop where function is depressed. As for the heart, its rhythm is disturbed by non-dangerous amounts of current, and the pulse will become rapid and somewhat irregular. Ventricular fibrillation, which is fatal in practically every instance (in experimental animals immediate counter shock may abolish the fibrillation) occurs when the current reaches an amount of something less than 100 milliamperes continued for a second or longer.

L. Alexander⁵ states as follows: "In hand to hand contacts cerebral changes are not due directly to the current but are caused by the prolonged circulatory disturbances produced by passage of the current through the heart and the endings of the vagus nerve."

Instances are known in which no loss of consciousness occurred, and the current pathway did not reach the brain, but within from a

few minutes to two or three days, the victim manifested signs of some focal reaction in the brain. As yet no satisfactory explanation has been offered for such delayed and distant tissue reactions.

If severe convulsions or prolonged coma are immediate effects of electrical shock, local cerebral circulatory reaction is not surprising. If there were a definite disturbance of heart function, or if a marked and prolonged change in blood pressure occurred, one might hypothesize some focal cerebral circulatory disturbance.

The literature cites instances of basal ganglia and other focal cerebral lesions as precipitated or due to electrical shock-effects in cases where the electrical current did not pass through or directly affect the brain. I will exclude from consideration the cases published without adequate evidence as to the physics involved or proper attention to the clinical facts. In a number of reported cases, the cerebral lesions are not progressive, and the clinical picture is not that of similar lesions due to other causes.

The trunk contains the great sympathetic ganglia and plexuses. If these tissues are directly affected by current traversing the trunk, it is physiologically entirely possible that stimuli from the splanchnic, celiac, and other abdominal sympathetic ganglia would have such an effect upon the great blood vessels in the trunk, that the circulation to distant parts of the body would be at least temporarily altered without any structural change whatever in these distant blood vessels.

It is known that stimulation of the cervical sympathetic ganglia affects cerebral circulation. Impulses originating in the trunk sympathetic ganglia undoubtedly may spread to the cervical sympathetic chain.

I have not found in the literature any discussion or experiments bearing upon this hypothetical physiological reaction.

However, such a reaction offers a theoretical basis to account for such distant reactions as those mentioned as producing even delayed focal cerebral lesions.

I. M. Schemker⁶ in a paper entitled, "Vasoparalysis of the Central Nervous System, A Characteristic Vascular Syndrome," presents certain conclusions which are perhaps germane.

I quote as follows: "Paralytic dilation of a blood vessel directly stimulated is accompanied by a slowing down of the blood stream which, if sufficient in degree, may result in stasis."

He quotes T. J. Putnam as observing that stimulation of cervical

sympathetic fibers causes an average reduction in blood flow of approximately 15 per cent, the systemic artery blood pressure remaining constant

He quotes Nedzel as observing that after injections of pitressin, "a typical picture of white stasis was observed" to occur in the adjacent region with associated degenerative lesions of perivascular nerve tissue

Scheinker commented also on the passive hyperemia observed in agonal states, and the instances in which great dilation of blood vessels is associated with structural changes of the vessel wall, resulting in increased permeability for serous fluid and red blood cells

Scheinker's paper is concerned chiefly with the effect of mechanical trauma on blood vessels. However, he points out that profound circulatory disturbances may be seen in regions remote from the direct influence of the irritant stimulus, thus indicating that the stimulus is probably transmitted over a neurovascular network to the distant subdivision of the vascular tree. If there is circulatory stasis, there is local accumulation of carbon dioxide which is a particularly active vasodilator. If it continues to accumulate, there is further vascular dilation and increased permeability of the vessel wall with actual degeneration and necrosis of the vessel walls if the alterations are sufficiently severe.

Thus, the essential vascular factor for involvement of surrounding tissues is the increased permeability of the vessel wall.

It has been amply demonstrated that the effect of electrical current on the blood vessels directly traversed is such that degenerative changes in surrounding tissue may be slow in development. It is an adage that electrical superficial burns may seem inconsequential at first, but that, due to delayed effects, there may be later extensive necrosis of the tissues injured.

If current traverses the cervical sympathetic, it is not unlikely that the brain vessels may be affected. If when the splanchnic and abdominal sympathetic ganglia are violently stimulated and there may be spread of the impulses to the cervical sympathetic, brain vessel reaction could occur. There might be immediate transient symptoms of focal nature if the brain vessel effects were limited to brief spasm. If the vessel wall were to suffer structural damage with impairment of permeability, effects on surrounding brain tissue might be delayed so that focal clinical symptoms would not be evident for even a few days.

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THE ROLE OF BILATERAL ORCHIECTOMY IN THE TREATMENT OF CARCINOMA OF THE PROSTATE GLAND *

A report of 82 cases

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INTRODUCTION

IN no branch of cancer research, since 1941, has the spotlight of medical interest been so definitely focused as that of carcinoma of the prostate gland. This interest was aroused by a series of brilliant experimental and clinical studies that fortunately appeared in a logical and orderly sequence. The series which was initiated by Kutscher and Wolbergs in 1935¹ with the discovery of large amounts of the phosphatase enzyme in the adult monkey and human prostate gland, culminated in the splendid experimental and clinical studies by Huggins and his associates^{2,3} on the effects of bilateral orchiectomy upon patients with carcinoma of the prostate gland. At last it seemed as though some of the mysterious factors controlling the development and especially the growth of carcinoma of the prostate gland had been discovered and a type of therapy based upon sound experimental and clinical observations and offering a very considerable degree of relief had been introduced. As a result, bilateral orchiectomy in the treatment of carcinoma of the prostate gland was accepted with enthusiasm by the medical profession.

Even before the report of Huggins and his associates others had observed the effects of surgical castration and irradiation sterilization upon patients with carcinoma of the prostate gland. Young⁴ had re-

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ported failures in two cases of carcinoma of the prostate gland following bilateral orchiectomy and Counsellor⁵ had observed a regression of metastases due to carcinoma of the prostate following sterilization by irradiation. Randall⁶ in 1942 reported a study of five patients who were castrated for carcinoma of the prostate, seven, eight, and nine years previously. Of these, one was living six and one-half years but had definite evidence of metastases. Munger in 1941⁷ reported eight patients treated by testicular irradiation, two of whom had had metastases of the pelvic bones six and three years respectively.

In the time that has elapsed since the report of Huggins and his associates on this type of therapy, many investigators have had an opportunity to observe its effects, conduct supplementary experimental and clinical studies, and report their findings. Excellent reports by Chute, Willetts and Gens,⁸ Nesbit and Cummings,⁹ Alyea and Henderson,¹⁰ Emmett and Hamm,¹¹ Dean, Woodard and Twombly,¹² and many others, confirmed for the most part the findings of Huggins and his associates. The question of hormonal inter-relationship between the testes and the prostate and pituitary gland was introduced in at least two of the above reports. Likewise the role of the 17-ketosteroids as an index of male hormonal activity was considered but no definite conclusions were drawn. Dean et al¹² suggested that fractionation of these might give valuable information concerning their biologic activity. The results obtained by Kretschmer¹³ in reporting eleven cases were apparently less satisfactory than those obtained by many of the other writers. In his series three patients were dead, five were not helped, two were improved, and one was reported as feeling well.

We were moved to review the results obtained by this method in our series of eighty-two patients not only because there seemed to be differences of opinion as to its effectiveness but for another, and to us a much more important reason. We were under the impression that some of our patients after orchiectomy had enjoyed a varying period of marked improvement that was followed by a relapse characterized by a rapid return to their condition before treatment or even worse. It was our hope that by studying the course of the patients treated by this method we might, in selected cases, be able to recognize and grasp a fleeting opportunity during the period of marked improvement, to obtain a much more satisfactory result by means of radical perineal prostatectomy.

RESULTS

The statistics which follow were derived from a study of the results obtained by bilateral orchiectomy upon 82 consecutive patients in various stages of development of carcinoma of the prostate gland in the period between January 1941 and June 1944

Age The 82 patients were studied for each decade of life and no relation was found between the age of patient and his response to treatment. The average age for all the patients was 69.4 years with a range of 55-84 years

Pathology The clinical diagnosis of carcinoma of the prostate was confirmed by microscopic study of stained sections in 59 of the 82 cases. Of these the tissue was obtained by means of a punch biopsy prior to orchiectomy in 29 cases. In the remaining cases the tissue was obtained at the time of transurethral resection for the relief of urinary obstruction. In 83.5 per cent of the cases the growth was predominantly adenocarcinoma while in 16.5 per cent it was predominantly a type of undifferentiated carcinoma. Sixty per cent of the patients in the latter group and 26.7 per cent in the former were known to be dead at the completion of this study

Acid and alkaline phosphatase studies Thirty-seven of the seventy-six patients upon whom serum acid phosphatase studies were made had normal preoperative readings. Of these the immediate (first two months) and remote readings remained normal except for one temporary slight increase in each category. There was no follow-up on two patients

The acid phosphatase readings were high before operation on thirty-nine patients. The results in these cases were: immediate drop (within two months) to normal, where it remained, fourteen; immediate drop to normal but remote increase to above normal, four; no immediate change but remote return to normal, three; immediate return to normal but no remote follow-up, four; no immediate readings but remote studies normal, two; very temporary increase followed by immediate return to normal, where it remained, two; immediate increase but no follow-up, one; and no immediate and remote studies in nine cases

Of the thirty-seven patients with normal acid phosphatase readings before operation eight were dead but at least three of these did not die from carcinoma of the prostate. Seventeen of the thirty-nine patients

who had high acid phosphatase readings before operation were dead. The survival rate was better than twice as great in the group with normal readings before operation.

At first we did not make a routine serum alkaline phosphatase study on our patients with carcinoma of the prostate because we believed that while it did indicate the response to bone injury it could give us little if any more information of prognostic value than we were able to obtain from our x-ray and serum acid phosphatase studies in our cases of carcinoma of the prostate. Later because we feared that we might be neglecting a source of considerable prognostic information, we decided to make serum alkaline phosphatase determinations.

Twenty patients had alkaline phosphatase studies made before operation. From the fifteen patients with normal readings before operation the following observations were made. Six maintained normal immediate and remote readings, four experienced an immediate increase but returned slowly to normal, three maintained an immediate normal reading but experienced a gradual increase, and two had normal immediate studies but no follow-up readings were recorded.

Five patients had elevated alkaline phosphatase readings before operation and the following observations were made. Immediate and remote readings remained about the same as preoperative in one, immediate increase followed by a drop and then a gradual steady increase in one, very temporary increase followed by a return to normal where it remained, one case, and two patients with an immediate increase had no follow-up studies.

Two of the five patients with elevated alkaline phosphatase readings before operation have already died of the disease. Three of the fifteen patients with normal preoperative alkaline serum phosphatase were dead when this study was completed.

We have elected to use as the normal for serum acid and alkaline phosphatase readings 0.5 and 0.10 King-Armstrong units respectively.

X-ray survey. The x-ray survey consisted of a routine check of the pelvic bones, lower end of the vertebral column, and upper ends of the femurs. More extensive studies were made when indicated. The results are shown in Table 1.

Comment. Fourteen of the twenty-six patients with positive x-ray studies for metastases were known to be dead at the time this study was completed. Eleven of the fifty-two patients with negative preoper-

TABLE I

RESULT OF X-RAY SURVEY FOR METASTASES IN 82 CASES

Positive before, no change	2
Positive before, progressed	13
Positive before, regressed	3
Positive before, no follow-up	8
Negative before, became positive	5
Negative before, remained negative	19
Negative before, no follow-up	28
No x-ray survey before operation	4
	82

TABLE II

TIME INTERVAL BETWEEN ORCHIECTOMY AND RESECTION

Time in months	1—2	6—12	18—24	24—30	Total number of patients
Number of patients	25	2	2	1	30

ative x-ray studies were known to be dead but at least three of them did not die from carcinoma of the prostate gland

Changes in the prostatic region The result of this therapy upon the prostate gland in eighty-two cases was as follows. Unchanged 26 per cent, regression occurred in 54 per cent, growth progressed in 2 per cent, and no follow-up report on 17 per cent. When the regression percentage was determined on the basis of the number of patients who had adequate follow-up rectal examinations, sixty-eight cases, it was found to be 66.2 per cent.

Operations for obstruction It was necessary after bilateral orchiectomy to perform a transurethral resection for relief of urinary obstruction upon thirty patients.

It is of interest to note that twenty-five patients required resection within two months after orchiectomy. It is possible that some of these resections could have been avoided if the patients had not been confined to their bed after orchiectomy, and the dosage of stilbestrol had

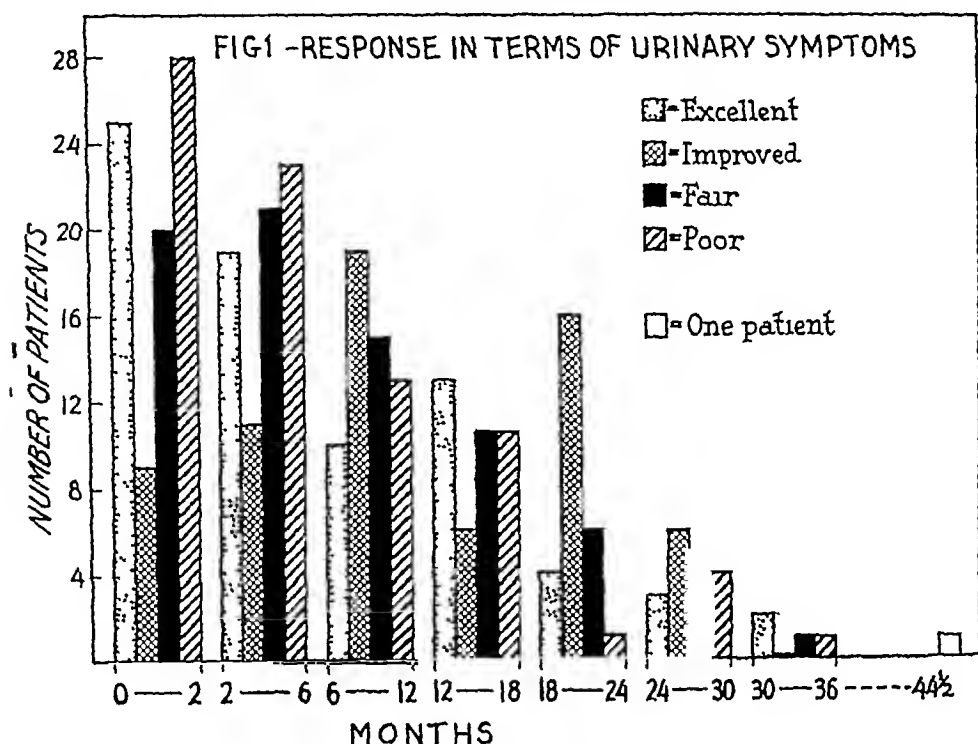


Fig 1 Shows the time intervals in relation to the response of the patients in terms of urinary symptoms. Explanation of terminology is as follows: excellent, patient is free from urinary symptoms; improved, symptoms present but minimal; fair, symptoms disturbing but not progressive; poor, symptoms are very disturbing and no response to therapy.

been materially increased. Of further interest is the finding in our data that within two months 35.2 per cent of the patients in the group without metastases had to have resections, whereas only 24.4 per cent of the group with metastases had to have resection.

Another interesting feature came to our attention during the study of the operative data. In the non-metastatic group, which included thirty-seven cases, nine patients had had a conservative perineal prostatectomy for urinary obstruction before orchiectomy, and at the completion of this study all were alive. In the metastatic group, which included forty-five patients, two of these had had suprapubic prostatectomy for obstruction before orchiectomy and both were dead.

General response to therapy In an effort to learn as much as we could about the effectiveness of this therapy upon the urinary and metastatic symptoms of the patients, their degree of response was estimated in terms of their condition at stated time intervals after

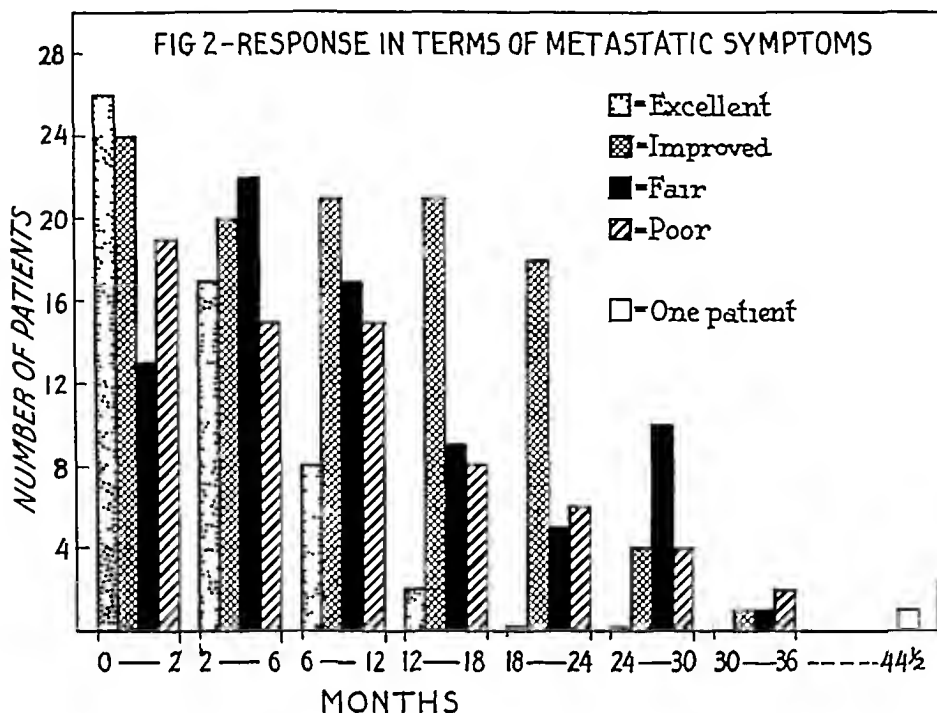


Fig 2 Shows the time intervals in relation to the response of the patients in terms of metastatic symptoms. Explanation of terminology is as follows, excellent, patient has no complaints, improved, definite improvement but not completely free of complaints, fair, improvement is slight but the disease is temporarily checked, poor, no response to therapy, and patient is incapacitated.

orchiectomy. On this basis the patients have been divided into groups according to their type of response which has been conveniently classified as excellent, improved, fair and poor (Figs 1 and 2).

Response in terms of urinary symptoms. A study of Fig 1 showed that the early response of the patients as estimated in terms of urinary symptoms was relatively slow, in fact twenty-five patients required resection for relief of obstruction in the first two months after orchiectomy. During the first six months period the number of patients in the improved grouping was relatively less than in the following six to twenty-four months, showing a delayed response to therapy in some cases. However, at the end of thirty-six months there were but few patients alive and these were in poor condition.

Response in terms of metastatic symptoms. A study of Fig 2 showed that the early response of the patients in terms of metastatic symptoms was much more pronounced after orchiectomy than in the case of

response to urinary symptoms during the same early period. The number of patients in the improved group continued rather constant through to twenty-four months. However, by the end of thirty-six months the results were quite similar to those obtained with respect to the urinary symptoms.

It is interesting to note that the number of patients in all groups in the 6-12 month period, both with reference to their response to urinary and metastatic symptoms, were about the same. However, at the end of thirty-six months only a few patients were alive in each classification and their progress was unsatisfactory.

When the response to therapy in terms of urinary and metastatic symptoms was considered in the light of the data presented by Bumpus¹⁴ in his study of a group of untreated patients, some interesting differences were apparent. He found that 485 patients with carcinoma of the prostate gland, who had received no treatment from the time of onset of the first symptoms until death lived an average of about thirty-one months. The average length of life in our series was 35.4 months, a slight but definite increase in the length of life as a result of therapy. He also found that 66.7 per cent of the patients having metastases at the time of examination were dead in nine months, while our study showed that 40 per cent were dead in an average of 15.1 months. In other patients without metastases at the time of examination Bumpus noted that their length of life was twelve months. Our patients without metastases lived an average of 17.1 months, in fact one of these lived 44.5 months. At the time this study was completed 31.7 per cent of all the patients were dead. Therefore, we have some statistical evidence in the above data that orchiectomy offered definite benefits when determined in terms of length of life.

DISCUSSION

From this study and a review of the literature there seems to be little doubt but that in the treatment of advanced carcinoma of the prostate, especially patients with symptoms of metastases, bilateral orchiectomy is a definite improvement over the therapeutic measures that were in use before its introduction. In the majority of these cases the immediate relief of pain, gain in appetite, increase in weight and the occasional decrease in urinary symptoms are often striking and most satisfactory. This clinical improvement is usually accompanied by

an immediate drop in acid serum phosphatase to or towards normal. If the alkaline serum phosphatase is elevated it may tend to increase for a short time and then drop toward or to normal. Of course there are unexplained exceptions to the above phosphatase reactions. In a small percentage of these cases there may be a temporary stop of the bony metastatic process or even regression. In a second and smaller group of patients the response to therapy is neither so marked nor so rapid but nevertheless it is definite and steady for a varying period of time. A third group, in which the response to therapy is at best only fair, is composed of patients who show but slight improvement or in whom the progress of the disease is apparently stopped for a time. In the last or fourth group are those patients who are not helped by this therapy. As the interval after treatment increases the number of patients in the excellent and improved groups steadily decreases so that when the period of between 24-30 months is reached the distribution of patients in each of the four response groups is about the same and very few are alive in any group. Therefore, while some patients are not helped by this therapy the majority obtain a varying degree of relief for a time and the average length of life after onset of symptoms and beginning of treatment is somewhat increased.

No study of the effects of bilateral orchiectomy is quite complete without a brief consideration of some of the untoward reactions that occasionally occur. The loss of sexual power while lamentable in the occasional case is usually a matter of secondary importance when viewed in the light of the patient's age and the marked improvement that sometimes results from this therapy. The unexplained swelling of the lower extremities that occasionally follows orchiectomy is usually quite temporary, disappearing in four or five months. The climacteric manifestations consisting of sweating, hot flashes, irritability, fatigue, etc., which occur in varying degree fortunately respond to estrogenic therapy. A postcastration gain of weight to an embarrassing degree is rare and was not seen in our series.

A great many of the reports on the effects of bilateral orchiectomy in carcinoma of the prostate have included observations on the beneficial results obtained from estrogenic therapy. Many believe that the response to this therapy, especially where large doses are well tolerated is quite comparable to that obtained by castration. In fact, Kahle and his associates¹⁵ in a most encouraging report observed among other

beneficial effects, the regression of metastatic lymph nodes in 2 cases. From our review of the literature and our own experience with these two types of therapy we are not as yet certain as to their relative merits. We do believe that in a certain group of patients in whom the response to one of these therapeutic measures is slower than average, the supplementary use of the other sometimes causes an immediate satisfactory reaction. Except in those instances where one or the other of these therapeutic measures is contraindicated, the decision as to which type should be used and when it should be instituted must await further clinical observations. Inasmuch as the majority of the patients in our series requiring an operation for the relief of urinary obstruction were operated upon during the first two months after their orchiectomy we are now using large supplementary doses of stilbestrol, when tolerated, especially upon those patients who evidently have considerable obstruction.

While the decision as to whether or not a patient is a suitable candidate for a follow-up radical perineal prostatectomy is frequently influenced by findings that are peculiar to each patient, there are certain fundamental requirements that should be met by all of them. In so far as one can determine from the patient's symptoms, x-ray survey and phosphatase studies there should be no evidence of metastases. The local lesion as a result of bilateral orchiectomy or stilbestrol therapy or a combination of both must be sufficiently reduced in size so as to present a reasonable chance for its complete removal. Finally the patient's physical condition should at least be fair and his life expectancy should be more than three years. The idea of attempting the radical removal of the primary lesion after orchiectomy has evidently occurred to others. Vallett in 1944¹⁶ reported a radical prostatectomy after orchiectomy for carcinoma of the prostate and a little later Parlow¹⁷ advocated the same procedure in selected cases.

In the 12 months that followed our decision to perform the radical prostatectomy upon patients who met the requirements previously stated, 5 were found upon whom the procedure seemed to offer a fair chance of success. Two of these had been treated by orchiectomy alone, 2 by large doses of stilbestrol and one by a combination of both types of therapy. Unfortunately up to the present time only 2 of them have been operated upon. One patient who was prepared for operation by a combination of both types of therapy was operated

upon by Dr A L Parlow, a member of our staff, and the other was prepared by stilbestrol therapy and operated upon by one of us At the time of operation in both cases it seemed as though all of the local lesion had been removed However, a study of microscopic serial sections made from both gross specimens suggested a strong possibility of at least a minimal extension beyond the field of operation Therefore while the immediate result in both cases appears quite satisfactory the remote prospects are rather uncertain It is our hope that at the very least the operation will prevent the occurrence of urinary obstruction and that it may greatly delay the development of a generalized process One patient, prepared on stilbestrol therapy, felt so well that he married and because of objections on the part of his wife, who is much younger, has refused surgery Of the two remaining patients who were prepared by bilateral orchiectomy one refused to have "any more cutting" and the other had a mild cerebral accident which seemed to make further surgery inadvisable Because it necessitates but one operation and avoids the climacteric nervous disturbances which frequently follow bilateral orchiectomy, we believe that these patients should be prepared for radical surgery, where possible, by stilbestrol therapy Furthermore in the event that it is impossible to remove the entire local lesion, bilateral orchiectomy could still be held in reserve for future use

CONCLUSIONS

- 1 A study of the results obtained by bilateral orchiectomy in the treatment of 82 patients in various stages of carcinoma of the prostate gland has been presented
- 2 In the majority of patients the early response of metastatic symptoms was much more rapid and satisfactory than had been obtained by the methods in common use before its introduction
- 3 The early response of urinary symptoms was neither so frequent nor satisfactory
- 4 A small percentage of patients received little or no benefit from this therapy
- 5 Most of the patients treated by this method were either dead or had lost its initial benefits within thirty-six months
- 6 In view of the discouraging end results following this therapy we believe that a follow-up radical perineal prostatectomy should be

very seriously considered, in selected cases, where the response to therapy is such that there is a reasonable chance for the removal of all or almost all of the primary lesion

7 As yet there is no substitute for radical perineal prostatectomy for cancer of the prostate gland where the patient's condition and size and location of the lesion at the time of the first examination permits its complete removal

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(Discussion on "The Role of Bilateral Orchiectomy in the Treatment of Carcinoma of the Prostate Gland" by Drs Scott and Benjamin follows on next page)

Discussion by DR JOHN S HESLIN (by invitation)

I want to express my appreciation for the invitation to open the discussion of Dr Scott's paper. His presentation is a valuable contribution at this time, and after reviewing a survey of our cases I can well appreciate the great amount of work his complete study has meant.

A review of our cases of carcinoma of the prostate in the Albany Hospital shows our experience to be similar to that of others who have reported their results. A bilateral orchiectomy with resection was routine procedure until recently and gives us a fair number of cases upon which to evaluate results.

The excellent results obtained in our early cases led to great enthusiasm, only to be followed by uncertainty as unrelieved cases and recurrences appeared. This survey tends to restore some of our confidence in the procedure as a valuable palliative measure in this serious disease. Recently we have performed orchiectomy only in the presence of definite pain due to metastases, or x-ray evidence of metastases, or an elevation of acid serum phosphatase.

An incidence of 15 per cent malignancy was revealed in our series of 376 cases undergoing transurethral resection this past year.

For this survey 96 cases of carcinoma of the prostate upon which orchiectomy was performed, between July 1, 1941 and September 1944, were reviewed by questionnaire and personal examination. Twenty-eight or 34.4 per cent were reported as having died, 21 failed to reply, 15 answered the questionnaire, and 32 appeared for examination. The following observations were made from this material:

*The effect of orchiectomy upon acid serum phosphatase studies
in 21 Cases*

16 Decreased	76.1%
4 Elevated	19.2%
1 No change	

The relation of x-ray evidence of metastases and acid serum phosphatase

X-ray positive for metastases	32 cases	
Elevated acid serum phosphatase	22 cases	68.75%
Decreased acid serum phosphatase	10 cases	31.25%

Effect of orchiectomy upon pain due to metastases (47 cases)

<i>Yrs Since Operation</i>	<i>Number of Cases</i>	<i>Pain Present Be fore Operation</i>	<i>Pain Relieved By Operation</i>	<i>Pain Recurred To Date</i>
3	1	1	0	
2 1/2	6	4	3	0
2	16	10	8	2
1 1/2	9	7	7	3
1	15	9	7	2
	<hr/> 47	<hr/> 31	<hr/> 25	<hr/> 7
		(65 9%)	(80 6%)	(28%)

Acid serum phosphatase was elevated in all cases of recurrence of pain

*Effect of orchiectomy upon the prostate gland
(32 cases examined by palpation)*

No evidence of malignancy	14	43 75%
Suspicious of malignancy	10	31 25%
Malignant	8	25%

As a result of this survey, we were impressed by the following

1 Number of glands with no evidence of malignancy upon rectal palpation (43 75 per cent of 32 cases examined)

2 80 6 per cent of 31 cases were relieved of pain, with a small number of recurrences

3 The excellent bladder function and general health in the great majority of patients

We are convinced that in this procedure we have a valuable palliative measure in the control of pain from the metastases of carcinoma of the prostate. Its value as a prophylactic measure, the stage in which it will give maximum results and its relation to stilbestrol therapy must await further clinical and biological studies

Discussion by DR HENRY G BUGBEE

Only through such papers as Dr Scott's will we be able to properly evaluate the role of orchiectomy in the treatment of cancer of the prostate. It is to be expected that those of us who have practiced urology for a considerable period of time will view any innovation in the man-

agement of this perennial problem with reserve and even a certain amount of cynicism. However, when one ceases to be open minded, his judgment becomes biased and he limits his sphere of usefulness to the patient.

Through the years many of us have at one time or another employed almost every method of treatment or operation, in an attempt to cure this disease. In some instances the results of treatment have been more distressing than the disease itself, such as the toxemia resulting from various methods of radiation and the mutilation often incident to efforts at surgical removal of the growth, or even of palliative surgery. Furthermore, we have noted a great variation in the course of the disease when untreated. The cancer in many instances is slow in its growth, such patients often living for years in comparative comfort. This leads us to interpret the occasional glowing accounts of a favorable course following operation or radiation as instances of a slowly growing type of cancer, cases that might have done well under any type of treatment or no treatment at all. Only through the treatment of a large number of cases and observations over a period of from five to ten years can one correctly evaluate any method of treatment for cancer of the prostate.

It is now some years since Huggins presented his studies, and most of us have treated a sufficient number of cases to have formed some fairly definite ideas regarding the efficacy of orchiectomy in the management of prostatic carcinoma. The striking and immediate improvement that has often been noted, especially in far advanced and disseminated cancer, gave promise of what some thought might prove to be a cure for this most difficult of urologic problems. However, sufficient time has elapsed and the number of cases so treated has mounted, so that I very much doubt if any urologist is willing to believe that orchiectomy can ever be considered a cure for cancer of the prostate. If, however, it does no more than give a temporary relief from pain, reduce the size of the prostate, soften the gland and improve the general wellbeing of the patient, as it does in so many instances, it has added much to our means of treating this distressing condition.

My own experience, observations of cases of other urologists and reviews of clinical reports, lead me to believe that the benefit derived from orchiectomy is temporary and is a procedure to be held in reserve until it is required to bring about the relief that we can usually expect,

namely relief of local pain from pressure or incident to metastasis, and to raise the general morale of the patient. If this operation is carried out early in the disease, the relief that it affords at a later period, when it is most needed, is denied the patient. I very much doubt if orchiectomy will reduce urinary retention, a phenomenon that has been noted following radiation.

The studies that have been carried out in blood chemistry associated with cancer of the prostate and the changes that have been recorded following orchiectomy are most interesting and give us corroborative evidence of the course of this disease, but from my own experience, such data would seldom provide an indication for orchiectomy.

Much has been written of late regarding total or radical prostatectomy for the cure of cancer of the prostate. If one encountered such a growth in a very early stage and it was so localized in the gland that a removal of gland and capsule would eliminate the cancer, such an operation would be ideal. The most favorable cases that I have encountered were those in which a small area of cancer was found on pathological section in prostates removed for hypertrophy and in which cancer was not suspected before operation. Eight such cases were reported in 1928. One subsequently died of cardiovascular disease, the others of cancer with definite local extension of the growth. I have seen perineal prostatectomy carried out by some of our most able surgeons for supposed cancer of the prostate and the hard nodule suspected of malignancy proved to be benign. I have seen also a prostate exposed, a suspected nodule excised, sectioned, found to be benign and the perineum closed. These procedures carried out by our most ardent advocates of this type of operative relief, make me wonder how often we really are able to select those cases most favorable for this type of operation. The various series showing results of radical operation that I have seen exhibited have not impressed me favorably from the standpoint of operative mortality, functional results and length of life, even though the operations were performed by our most skilful perineal surgeons. To my mind their results do not compare favorably with the symptomatic relief obtained through the elimination of retention by transurethral resection and the employment of orchiectomy to alleviate the pain, local and general, due to metastasis late in the disease.

A patient now 84 years of age who has been under my care since 1918, at which time he had an unmistakable cancer of the prostate.

went on comfortably until 5 years ago when he developed retention Transurethral resection gave relief and he now attends daily to an active law practice, voids once at night, every 4 or 5 hours during the day and says he is comfortable I still have orchiectomy to offer him when the symptoms warrant I could cite other cases that have been observed over shorter but appreciable periods of time, in which the growth has progressed slowly Sulfa drugs have played an important role in controlling infection and stilbestrol has occasionally served as a valuable adjunct

These brief remarks are not intended as a deterrent toward any one method of treatment of cancer of the prostate, but from the facts at hand I do not believe that we are yet in a position to talk about cures in this disease This does not mean that we should not make every effort to detect those cases which might be cured, especially through an attempted complete removal Rarely such cases may be encountered. In recording such a result, however, one cannot lose sight of the cases which have often shown little change over a long period of years and wonder if the case reported might not have been such a type of growth The advisability of attempting prostatectomy following orchiectomy can only be evaluated following its trial in a series of cases, observed over a sufficient length of time

At the present time I believe that we should give these cases the benefit of what we think will give the individual the greatest relief over the longest period of time, and in this role orchiectomy has established a very definite place

Dr Scott has given us a clear, comprehensive, unbiased report of his wide experience with this operation His remarks will add considerably to our knowledge and we are indebted to him for them

Discussion by DR OSWALD S LOWSLEY

I enjoyed Dr Scott's paper very much We all know that cancer is the black page in all phases of medical practice The etiology of prostatic carcinoma is unknown, but our observations lead us to believe that Huggins and Munger are on the right track when they state that there is a relationship of the androgenic hormone to this type of cancer Yet as time elapses, we find that while castration is very helpful in many cases, it is not the complete answer to the cancer problem

In our department at New York Hospital we try, in all controversial

matters, to give each member of the department leeway to do what he thinks best. Thus we have one group which has done castration on every case of cancer of the prostate, another which has done it only when pain develops, and so forth. A great mass of statistics is necessary to arrive at characteristic findings, even though it may seem quite confusing at times. So far, the number of our cases is not sufficient for definite conclusions. However, Dr. Pavlow, our resident, has gathered together some statistics on 276 patients who have come under our care. From these we have made certain observations, briefly as follows:

1. Prostatic carcinoma seems to be of two types. The large majority (over 75 per cent) begin in the posterior lobe. The remainder are found in adenomatous hypertrophies which have been removed, their presence being unsuspected until revealed by the microscope. A morphologic peculiarity of these cancers is the diversity of their forms. Adenocarcinoma is the commonest type, but scirrhus, medullary, and squamous cell carcinoma may be found, sometimes in the same specimen. The frequency of metastases to the pelvic bones and the lumbar vertebrae is well known. However, dissemination may also occur in distant areas.

2. These cancers not infrequently occur in men who are under the age usually associated with benign hypertrophy, that is, 50 years and over. Of our 276 patients, the youngest was 45 years and 4 others were under 50 years of age. The greatest incidence (42 per cent) was in the sixth decade.

3. The symptoms of prostatic carcinoma occur late and are not easily differentiated from those of adenomatous hypertrophy. Over 50 per cent of our patients had symptoms less than one year. Urinary disturbances, usually the first symptoms, were present in all but 12 of our cases. Pain, which often is due to skeletal metastases, was present in 63 cases, hematuria in 61, and loss of weight in 34. These are all late manifestations and not helpful in diagnosing the condition early. Four patients with quite extensive carcinomas had no symptoms whatsoever, their tumors being discovered during physical examinations for other reasons.

4. Over one-half (56 per cent) of our cases were diagnosed by rectal palpation. In doubtful cases, microscopic examination of tissue removed from suspicious areas with a biopsy instrument introduced through the perineum successfully establishes the diagnosis as a rule.

Carcinomas coexisting with adenomatous hypertrophy may be very difficult to diagnose clinically

5 We have found acid serum phosphatase studies very helpful in determining the presence of skeletal metastases, and as an index to the progression of metastases. In cases having 10 or more King and Armstrong units per 100 cc of blood, definite x-ray evidence of such metastasis either is present or is likely to develop subsequently

6 The prognosis of prostatic carcinoma is grave. In early tumors which have not extended beyond the prostate and its capsule, radical removal of the prostate and seminal vesicles, plus castration by the method described above, would seem to offer the best hope of a cure of the disease. In cases where the growth has extended beyond the limits of the prostate, total prostatectomy without the removal of the seminal vesicles, plus castration, will usually relieve the patient's symptoms and prevent recurrence of the disease at the bladder neck, and thus the patient will not die of the effects of urinary obstruction. Stilbestrol is helpful when castration is not permitted.

7 Regarding treatment, it is difficult to summarize these statistics, but the following is clear:

From 1921 to 1938, a period of 17 years, various forms of treatment were utilized, for the most part open operation and implantation of radon seeds, often with supplementary deep x-ray therapy. Eighteen out of the 165 patients are known to have lived 3 years or longer, one hardy soul being alive 8 years after a transurethral resection with radon implantation and deep x-ray therapy.

From January 1938 to January 1944 there was a total of 111 cases: 64 without castration and 47 with castration. Of the former, 44 patients with prostatectomy or resection were followed up. Thirteen of these lived 3 years or longer, all after open operations. The longest survival was 5½ years. This patient is still alive and quite well.

Of the 47 patients who had castration, 20 were alive on January 1, 1944: 8 after open operation and castration, 16 after transurethral resection and castration, and one after castration only. One cannot draw definite conclusions regarding improvement in the mortality rate of the castrated cases as compared with the non-castrated cases because insufficient time (only 3½ years) has elapsed since this method was instituted.

In our experience the procedure has not made very much difference

in the sexual powers, perhaps because most of these patients are beyond the age of sexual activity. Eunuchs in the Far East have been known to retain their sexual vigor for many years after castration.

There is no doubt but that the castrated patients show a prompt and often complete freedom from pain, gain weight, and have a feeling and appearance of well-being. This last is heightened by the splendid cosmetic effect produced by the implantation of fat into the tunica albuginea after removal of the testicular tissue as described above. Even should it turn out, as it well may, that life is not remarkably extended by the addition of castration to our armamentarium, this procedure is still worth while, because it is our duty as physicians not only to preserve life but to relieve suffering, and castration in carcinoma of the prostate unquestionably does that.

Again may I say that I appreciate Dr. Scott's paper. It is a very accurate statistical study, and we are indeed fortunate to have had it presented to us.

Discussion by DR. ARCHIE L. DEAN

After reading Dr. Scott's excellent paper and having had the opportunity of hearing him present it, one must praise his work because it consists of a sizable number of patients carefully studied. The men studied were apparently in about the usual condition of patients commonly seen with prostatic cancers, and responded to the treatment he gave them in about the same way that other similar groups have reacted to the most careful endocrine treatment. The only points of Dr. Scott's work which are not quite clear to me are—

1. When, in addition to orchiectomy, did he employ stilbestrol?
2. Why did he use this drug, and
3. In what way did stilbestrol, superimposed on castration, modify the patient's clinical course?

At Memorial Hospital we have been able to treat and observe over reasonably long periods 120 patients with histologically proved prostatic cancers. Additional patients were treated but, for various reasons, they were unsatisfactory for close study. On the basis of our experiences and the work of others there appears to be a close similarity in the clinical picture presented by every comprehensive series of patients with prostatic cancers treated by modification of the endocrines. This makes the work of all reporting urologists more convincing.

On the basis of their response to treatment we recognize in a rough way, three groups of patients

Group I There is a small minority of men who, in spite of all treatment, follow an uninterrupted downhill course ending in death

Group II The great majority are benefitted Speaking generally and somewhat optimistically, pain is relieved promptly and completely, appetites are much improved, physical and mental ability is reestablished, the primary tumor softens and shrinks, and metastases in soft parts including even large secondary deposits in the lungs, disappear until all in all a remarkably favorable transformation has taken place After a varying period of good health (between 7 and 9 months in our patients) the majority, about 60 per cent, relapse and the disease progresses at a rate apparently more rapid than before treatment was first given, until death occurs We have been unable to significantly alter this fatal outcome by administering stilbestrol to castrated patients or by castrating those men treated primarily with stilbestrol

Group III The remaining patients who survive the period of common relapse may continue indefinitely longer in seemingly good health but in one by one the prostatic cancers appear to become reactive and they succumb During this period it is also possible, as Dr Scott stated, for patients to die of intercurrent disease There may be a few individuals who continue well A small number of our patients show no disease, excepting perhaps long unchanged x-ray evidence of bone metastases, for more than 3 years after treatment was started One does not know as yet what their future development will be

When we first began to treat cancers of the prostate by modification of the endocrines, alternate patients were treated by castration and by the administration of stilbestrol After observing the results on nearly 80 patients the administration of stilbestrol 1 mg daily by mouth at bed time became and has remained the primary treatment of choice Comparison of these two types of treatment in our hands shows that castration often produces a spectacular disappearance of bone pain in 24 to 48 hours whereas 1 mg daily of stilbestrol requires 7 to 14 days to bring about this result although large initial doses of estrogens in the form of pellets may equal the immediate effects of castration Other than this we have observed no feature of the disease which was not as greatly improved by the drug as by operation nor have we found reason to combine the two treatments

Because Dr Woodward, physiological chemist of the Memorial Hospital, was one of the pioneers in demonstrating the significance of the phosphatases in cancers of the prostate and in other diseases, we have for years supplemented clinical observations on patients with prostatic cancers with frequent assays of the acid and alkaline phosphatases of the serum and have become convinced of their diagnostic and prognostic value. Although there is little clinical difference between the prostatic cancers of castrated patients and those treated with stilbestrol, phosphatase studies suggest that the results are brought about by different processes. After castration the acid phosphatase quickly drops to normal or nearly normal. When bone metastases are present, the alkaline phosphatase at first increases in 66 per cent of the patients. After about 2 months it decreases to far below the initial reading. This suggests that during endocrine rearrangement following castration there is some change which stimulates bone regeneration. Since alkaline phosphatase rises after castration in other diseases with bone metastases, we believe this reaction is a bone reaction rather than a prostatic cancer reaction, in other words, it is a reaction of the bone around the tumor rather than a reaction of the cancer metastasis in the bone.

When stilbestrol is administered the serum acid phosphatase decreases to normal or toward normal, but not so rapidly as after castration. In the presence of bone metastases there is an initial rise of alkaline phosphatase in only 20 per cent of cases. This is followed by a gradual fall.

In general, phosphatase studies suggest that after either castration or stilbestrol there is a change in the metabolism of the prostatic cancer characterized by a diminution of the acid phosphatase.

We have experienced difficulty in recognizing x-ray evidence of changes in bone metastases during and after treatment. Since the pictures we have seen have changed slowly, if at all, we depend exclusively on measurements of the serum alkaline phosphatase to show the immediate status of bone lesions. This test appears to be quite sensitive for the purpose.

From the fact that there is general agreement concerning the clinical response of prostatic cancers to endocrine treatment it would appear that urologists have well performed their functions of administering the best treatment known and observing its effects accurately. Even so, unfortunately, the treatment of this important disease remains em-

pirical because one does not know how to choose the most effective treatment for the individual patient nor can one accurately predict his response. I believe the answers to these and many other questions of equal importance will be solved by steroid chemists after they succeed in isolating the different androgens and estrogens and learning the physiological functions which each performs.

Discussion by DR E GRANVILLE CRABTREE

It has been a great pleasure to be present as a guest of the Society this evening. I have enjoyed Dr Scott's paper very much indeed. It has a definite place in the long series of attempts which are being made throughout the country to establish an exact basis for applying the important contribution of Huggins for the treatment of cancer of the prostate for the best interest of the patient. It has not been easy to arrive at that end.

Progress towards this end has been delayed by unfortunate lay publicity which is so freely given in medical matters nowadays, such as the publication by DeKreif on this subject some time ago. The unwarranted optimism there expressed is not now borne out by present facts. It has been necessary for urologists, from that time on, to combat (often unsuccessfully) the patient's conviction that the endocrines are curative. I have also attempted to influence patients to permit total prostatectomy after apparent disappearance of cancer under hormonal therapy, only to find that articles in the lay press stood in my way. Dr Scott's incidents of similar nature indicate that I have not been alone in this. Not one of my patients would consent to operation, which might have been curative in the stage of improvement. The lay press assumes perhaps unconsciously the role of advisors without responsibility—a dangerous situation in any field.

I shall watch with interest developments which follow the recent story of the Smithwick operation in *The Saturday Evening Post*. This new and as yet not fully established procedure is now similarly placed in this subject of prostatic cancer. The surgery for the condition is difficult and few adequately trained surgeons capable of the operation exist at the time wide publicity creates wide demand.

I wish the lay press would allow us time to establish more nearly the value of new procedures before they rush publicity which is capable of doing great harm.

Discussion by DR CLYDE L DEMING

Dr Scott's paper has been extremely interesting, and I appreciate the honor of being asked to discuss it. I shall confine myself to just a word of comment.

Briefly, we accept three main facts in the consideration of the results of hormonal therapy for cancer of the prostate: (1) Pain is relieved in 80 per cent of cases in which there are metastases; (2) About 60 per cent are improved as far as general wellbeing of the patient is concerned; (3) As far as we know, no case has ever been cured by hormonal therapy alone. That leaves us with the necessity of doing a radical extirpation of the prostate in those cases where the tumor is limited to the prostatic capsule.

The future approach to this problem lies along two avenues. First, there is that of clinical study on the part of the urologist. He must find out when and how much of the hormone to give. The second point may be a far-fetched idea, but I believe that it lies just ahead of us, that is, to give hormonal therapy as a prophylactic so that no one will develop a prostatic cancer. This latter avenue must be approached through the biochemist. He must first tell us what the carcinogenic agent in the testis is which causes a stimulation of the epithelium of the prostate to grow into a cancerous condition. He must also find out, if possible, what anti-carcinogenic is present in stilbestrol or similar substances.

Dr Scott has made an approach to these problems clinically. He is attempting to give us a procedure which will make an inoperable case an operable one. First, he reduces the cancerous growth, then removes it in those cases in which it seems indicated. Certainly one should not attempt a total removal of the prostate if there is an elevation of the acid serum phosphatase.

In support of Dr Scott's contention that if it is possible to reduce the size of the prostate by hormonal therapy, surgical removal should then be advocated, I would like to remind you of a case reported by Dr Herbst of Washington. It is only a single case, but a very interesting one. The case was one of an undoubted carcinoma of the prostate proved by biopsy. While extensive hormonal therapy left the glandular tissue greatly reduced, even to normal size, soft and elastic to palpation, yet after the patient's death from coronary disease or pneumonia (I forget which) autopsy showed in the center of the prostate a small nest of visible cancer cells.

DR SCOTT (Closing)

First I want to thank Dr Delzell and the members of the New York Society of the American Urological Association for the privilege of presenting this paper, in which Dr Benjamin joins me. Also we greatly appreciate the courtesy and consideration shown us by those who have discussed the paper.

We agree with Dr Bugbee that because it is seldom possible to determine in advance with any degree of accuracy the course of a patient with carcinoma of the prostate gland it is difficult to decide upon the type of therapy to use and to evaluate properly its effect. In our series, 60 per cent of the patients with the predominantly undifferentiated type of carcinoma of the prostate and 26.7 per cent with the predominantly adenocarcinoma type of tumor were dead when this series was completed. A histological study of tissue from the prostate might give some information as to the prognosis of the patient and the type of therapy that would be of most value. It would seem that Dr Bugbee's evaluation of the radical prostatectomy in the treatment of carcinoma of the prostate is definitely different than ours. It is only by such honest difference of opinion that truths are determined and medical progress is made.

We agree with Dr Lowsley concerning his uncertainty with reference to the relative merits of orchiectomy and estrogenic therapy. We are of the opinion that in certain cases where the response to one type of therapy was not quite satisfactory the supplementary use of the other sometimes proved to be quite beneficial. In one of our cases in which the effect of orchiectomy was not sufficient to permit a radical follow-up prostatectomy, the supplementary use of stilbestrol made this procedure possible.

In answer to Dr Dean's query as to the factors that aid us in making a choice between orchiectomy and stilbestrol therapy we can only state that we are governed by no set rules in this respect but rather by the findings in each case. For example, one of our patients who had a history of a coronary thrombosis three months previously had an involvement of the prostate, when first seen, that seemed a little too extensive to permit its complete removal without preliminary shrinkage. Because of his cardiac history and the findings it seemed advisable, if possible, to prepare him with stilbestrol therapy. His response

to this treatment was so satisfactory that it was possible to perform a follow-up radical prostatectomy. In such cases, where a moderate decrease in the size of the prostate gland will permit a radical prostatectomy it is probably wise to try stilbestrol therapy first. We are of the opinion that if we had used stilbestrol therapy in preference to orchiectomy in the patient who refused to have "any more cutting" he might have consented to a follow-up radical prostatectomy.

The results obtained by Dr. Heslin in the very excellent review of his cases of carcinoma of the prostate gland treated by orchiectomy confirm the results obtained by us and others by this therapy.

It is much too soon to know what will happen to these patients who have had a follow-up radical prostatectomy after preliminary bilateral orchiectomy or stilbestrol therapy, but we hope the results will be an improvement over those obtained by orchiectomy or stilbestrol therapy alone or in combination. It is our intention to try this combined therapy upon a series of patients and it is our hope that others will do the same and report their results.

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BULLETIN OF
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JULY 1945

INFLUENZA
METHODS OF STUDY AND CONTROL¹

The Wesley M Carpenter Lecture²

THOMAS FRANCIS, JR

THAT influenza should be chosen as the subject for the Wesley M Carpenter Lecture is a signal distinction and a recognition of the developments in the field during the past decade. In this time we move from the first identification in the Western Hemisphere of virus from epidemics of influenza in man, to the demonstration that prophylaxis against the epidemic disease is possible. In the advance there have been numerous contributors, many diversions and frequent discoveries of fundamental biological importance.

The probabilities for the control of an infectious disease increase as knowledge of its biology advances. There is no simple formula leading to a successful conclusion. Once the responsible agent is identified, however, information develops as tools and methods for promoting the study are devised. But in the study interest in the method should not

¹ From the Virus Laboratory and the Department of Epidemiology, School of Public Health University of Michigan. Certain of these studies were conducted under the auspices of the Commission on Influenza Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army, Preventive Medicine Service Office of The Surgeon General U S Army.

² Given October 13, 1944 at the Seventeenth Graduate Fortnight of The New York Academy of Medicine.

obscure the problem of the disease its identification, an understanding of the mechanisms by which it is produced, maintained, and distributed, an evaluation of procedures which might aid in the control or cure of the disease

Since 1933, when Smith, Andrewes and Laidlaw,¹ following on the heels of Shope's² demonstration that a virus was involved in swine influenza, first identified a virus from human influenza, a large number of investigators in numerous laboratories in different countries have tackled the various aspects of the problem. While it is impossible to make a sharp division between studies of the virus and the application of this information to study of the natural disease it may be well first to review certain characteristics of the virus which serve as the basis for much of the wider research

STUDIES OF THE VIRUS

Media At present there is no direct method for the rapid identification of influenza virus in the clinical case. Its recognition depends upon the demonstration of effects produced in the course of its infectious activity. At first the response of the ferret was the sole indicator, then the mouse, squirrel, hamster and other species came into use. Later the embryonated hen's egg became important, with infection established by inoculation onto the chorioallantoic membrane, into the amniotic sac, directly into the embryo, or simply of unfiltered throat washings into the allantoic sac. Beyond a characteristic febrile reaction in the ferret, demonstration of the virus' presence in animals, after intranasal inoculation of suspected material, comes from the development of a typical pulmonary lesion with continued passage or through the fact that the virus induces the production of antibodies in the blood and a state of resistance to reinfection. Originally the egg had somewhat the same general purpose as tissue cultures, for demonstration that virus was present depended upon secondary transfer to animals or serological procedures. In the important discovery first reported by Hirst,³ later also by McClelland and Hare,⁴ that influenza virus caused agglutination of erythrocytes of the embryonic or adult chicken an extremely adaptable reaction came into use. When a certain concentration of virus in the egg is reached it can be readily indicated by an immediate macroscopic effect. The possibility of rapid identification of influenza virus in the patient's secretions has been thereby enhanced so that in at least

two instances the actual nature of an outbreak was established in about 4 days by inoculation of eggs^{5, 6}

Antigenic Variation Two types of virus are at present identified Type A is the group of strains resembling the original WS strain of 1933 Strains of swine influenza also have antigenic relationship to Type A virus^{7, 8} For a period it appeared on the basis of procedures employed at the time that the strains were antigenically identical but, together with Magill in 1937,⁹ it was shown by more precise methods that even the strains exhibited detectable variations As these studies expanded, more striking differences among them became apparent¹⁰ In the eggs the strain differences appear to be accentuated to such an extent that it represents one of the hazards of the method On the other hand there is the possibility that the antigenic status as determined early in the egg is more truly representative of the human virus as it moves at large than that adapted to animals by repeated passages Burnet has suggested the significance of still finer differences He noted with one strain adapted to eggs by the amniotic sac that there was a greater capacity to agglutinate guinea pig cells than chick cells and that by selective adaptation, only agglutinins for guinea pig cells were developed¹¹ Under other conditions the agglutinins for chicken cells developed and overgrew the cavean agglutinins He suggested that the guinea pig agglutinins were those of the original human strain -O- while agglutinins of chicken cells were the result of a derivative -D- developing in the egg—thus a variant of the original These interpretations do not appear to be supported in the observations of Rickard and his associates or those of our laboratory where virus has been identified after its first inoculation into eggs, by the agglutination of chicken cells to a high titer without significant differences in its effect on guinea pig cells¹² Although certain of the variations detectable by increasing refinements in technique seem to be of academic interest, evidence continues to accumulate indicating that they are of practical importance as well

Type B influenza virus was discovered in 1940 but evidence showed that it had been prevalent in the epidemic of early 1936^{13, 14} Its general behavior in animals and eggs is essentially the same as that of Type A It has, however, been consistently milder in its pathogenicity for animals and relatively few strains of the virus have been isolated But despite the otherwise close similarities, immunologically Type B virus

is so distinct from Type A as to represent an entirely different agent. The difference is much greater than the variations between strains of Type A so that hyperimmune serum which largely obliterates strain specificity and overlaps the boundaries between Type A and swine viruses fails to show cross reactions between A and B ¹⁶

The importance of these sharply distinguished entities to an understanding of the disease problem will be clearly seen later in the discussion

Serological Reactions In response to exposure to influenza virus, whether by infection or otherwise, antibodies which may be measured in a variety of ways can be demonstrated in the blood stream. The capacity of the virus to infect animals can be neutralized by mixing it with serum of the recovered animal, the neutralizing or protective antibodies are most commonly measured in mice by determining how little serum added to a known amount of virus is required to prevent infection when the mixture is given intranasally. In this manner it was first shown that a large percentage of human individuals after the first few years of life, presumably as a result of natural infection, had antibodies to influenza A ^{16, 17} and that despite this fact they might well acquire the disease again with a further rise in titer. The response was so clearly correlated with infection by Type A influenza virus and not with other infections that its specificity was established ¹⁸. Infection with Type B virus has no influence on the titer to A, and vice versa ^{13, 14}. And now the demonstration of an increase in titer between serum taken in the acute phase of illness and that in convalescence is generally diagnostic.

Recently, Hirst's observation ¹⁹ that antibodies to influenza virus would prevent the virus from agglutinating chicken erythrocytes has resulted in still more simplified serological procedures, which can be carried out rapidly in a general laboratory.

It is interesting in this respect that here again there is a sharp specificity between Type A and Type B viruses in that the respective immune sera inhibit only the homologous virus from causing agglutination.

It is not desirable in the scope of the present discussion to dwell too long on these measures of the virus activity although they represent largely the underlying methods upon which much of the subsequent information is based. There are other lines of physico-chemical

research which have been increasingly attractive. The size of the virus has been measured under a variety of conditions and except for one brief excursion into much smaller realms its diameter is at present still somewhere between 70 to 100 μ ^{20, 21, 22, 23}. Efforts to characterize the virus by electron microscopy have yielded photographs of rounded bodies with relatively high homogeneity which appear to possess the virus activity^{22, 24, 25}. The active component freed from much extraneous material has also been obtained in sufficient amounts to foster attempts to identify the chemical composition of the influenza viruses. But at the risk of appearing to minimize the importance of these splendid studies of fundamental biological significance, I should like to turn to the body of investigations which are more concerned with the clinical and epidemiological aspects of the disease.

PATHOGENESIS

An understanding of the mode of action of influenza virus is important since it serves to orient many activities which might appear at first glance unrelated. Investigation shows that influenza viruses act quite specifically upon the respiratory tract. Except that certain strains have been shown to be adaptable to the nervous tissue in mice^{26, 27} and that an hemorrhagic encephalitis, similar to that produced by many viruses, is observed in infected chick embryos,²⁸ influenza virus in swine, ferrets, mice, chick embryos and man exerts its pathogenic effect on the epithelium of the respiratory system. When virus is administered in relatively large amounts by pararespiratory routes, the disease is not produced whereas a minute amount intranasally sets up the infection. The injury is largely a destruction of the typical ciliated columnar epithelium which lines the larger respiratory divisions and which the virus reaches ordinarily by entry into the lumen. This is the essential tissue to which protection must be furnished in order to prevent disease. When moderate amounts of virus are given intraperitoneally or intravenously to mice, virus can be recovered from the lungs but pulmonary lesions do not develop. This is probably accounted for by the fact that the virus is on the wrong side of the susceptible cell and only when it floods over into the upper respiratory tract will it gain access to the epithelial lining. The pneumonia which develops in experimental animals, while related to the virus injury, is apparently a lesion secondary to epithelial destruction and the subsequent serous exudation.

The effect of bacteria upon the pathologic process in man is not well known since influenza of recent years has not been associated with a high incidence of complications. In several instances, however, observers have discovered simultaneous prevalence of influenza A or B and hemolytic streptococcal infection without too great evidence of symbiotic effect.²⁹ Shope has clearly shown, however, the exaggeration of injury produced when swine influenza virus and *H. influenzae suis* are given together.³⁰ A mild illness is converted into a serious disease. As yet unpublished studies from our laboratory have demonstrated in mice that strains of *H. influenzae*, which by themselves are harmless intranasally, when given several days after a minimal non-fatal virus infection is induced, can establish themselves, multiply and bring about a lethal result. Moreover, it appears that in some instances the virulence of the bacterial strain is enhanced.

It is apparent, however, that the virus is the major component in the origin of influenza and the disease which has been studied in man has been largely an uncomplicated infection. Consequently, much of the discussion deals with information gained under these conditions in relation to specific cellular injury by the virus.

THE CLINICAL DISEASE

During the course of an epidemic of influenza there is a surprising degree of uniformity in the clinical picture presented. Nevertheless, studies of the virus infection reveal, as with most diseases, that severity varies from the unrecognized subclinical invasion in a relatively large proportion of the population to the severe fatal disease in which pulmonary involvement is prominent. But that they represent infection by the same virus has been amply demonstrated by the recovery of the virus and by a study of the serological responses.

On the basis of studies in the past decade influenza A tends to elicit a sharp clinical disease with abrupt onset, fever and pronounced constitutional symptoms of three to four days' duration. Even in the milder cases the course tends to follow the same pattern. On the other hand several reports have noted that in comparison influenza B has had a more gradual onset,^{31, 32, 33, 34} the disease was less intense and the duration of the fever shorter. Several of the writers describe the onset as a common cold and some observers have noted in children, especially, almost an absence of significant complaints. These impressions are sub-

stantiated to some extent by our experience with a group under close observation. Influenza B occurred in nearly 25 per cent of the population in a large institution as demonstrated by serological means although only 4 clinical cases were recognized.³⁵ However, the epidemics of influenza B which were studied in 1936 and 1940 revealed a large body of cases with clinical illness quite typical of epidemic influenza.^{13,31} Nigg and her associates reported 4 cases of fatal pneumonia during a limited outbreak of influenza B.³⁶ In a prevalence a year ago among a group of 100 elderly women, three fatalities occurred out of thirty-one cases. One point noted in the 1936 and subsequent epidemics of influenza B which differed somewhat from that usually seen in influenza A is the not uncommon tendency to nausea and vomiting.

Further evidence of the clinical features has been gained from infection experimentally induced in human subjects by inhalation of virus.^{37,41} It is quite striking that while signs of parenchymal involvement have been noted in a proportion of cases, pneumonia has been a rare complication. The incubation period with experimental influenza A has been 24 to 48 hours and the onset abrupt. Chills or chilliness, fever, cough, headache, general aches and prostration of two to three days' duration have been the rule. Nasal discharge has been less frequent. A considerable degree of lassitude follows the decline of fever. With experimental influenza B the incubation period has in general been shorter, not uncommonly twelve to eighteen hours. This brief incubation period is a striking observation and that it represents the effect of active virus is seen by the fact that irradiated material does not produce clinical disturbance. In addition, the course of experimental influenza B has been milder than that of influenza A, fever has usually been of no more than one day's duration and recovery appears to be more rapid. Even under these circumstances nausea and vomiting has been not infrequent.

The illnesses produced by these two viruses offer certain contrasts with the form of upper respiratory infection most commonly associated with atypical pneumonia. It is quite certainly *not* influenza A or B. The onset is usually much more gradual with symptoms of respiratory irritation appearing early. Nasal congestion, cough, hoarseness, sub-sternal soreness tend to develop progressively but the patient does not usually present the same degree of prostration. The leukocyte count is not so uniformly low. While these differences appear to be of minor

nature, they tend to be quite prominent when seen in large groups

In the individual patient, however, because of the wide variations that may be encountered the difficulty in diagnosis is increased. And since many of the symptoms can be found related to the onset of a great number of diseases, there is still no simple test which permits a prompt diagnosis at a single glance. Efforts which seek to find specific clinical methods for identifying the various etiological entities have revealed the probability that still other types of influenza virus will be discovered, and that unrelated viruses will be found in some of the respiratory infections which at present prevail. The importance of gaining this knowledge cannot be overemphasized since it constitutes the information through which specific preventive or curative measures can be devised.

EPIDEMIOLOGY

Just as identification of influenza virus infection serves to chart the clinical boundaries so it is a valuable procedure in giving information as to the natural history of the diseases, for in this manner the wanderings of the virus can be detected even when they are not suspected through clinical or epidemiological observation. For several years, together with other investigators, it was my opinion that influenza A was almost exclusively an epidemic disease. This was based to a large extent upon the fact that the periods in which the virus had been shown to be present were occupied by epidemics. Moreover, for nearly nine months in 1940 a constant sampling of respiratory infections in the wards of the Third Medical Division, Bellevue Hospital, was made by I. J. Brightman.⁴² The first case of influenza A was identified at the end of this period in December when an epidemic began in the city. There was thus little evidence of scattered sporadic cases.

From the winter of 1932-33 when the virus was first isolated until 1940-41, five outbreaks in alternate years had been identified. The cycle skipped a beat in 1942-43 and the epidemic appeared last winter after a three-year interval. But despite the fact that the usual epidemic did not occur during the winter of 1942-43, influenza A was found to be in operation. In Canada, Hare and others observed a sudden, self-limiting, brief flurry in an Army group in April 1943,^{33,43} in England, spotty group infections unrelated to any general incidence were detected during that summer.⁴⁴ In Australia scattered cases were detected in the

same months ³⁴ In our studies serological evidence was obtained of three possible cases in February and March while in May, 3 definite cases, from one of which virus was recovered, suddenly appeared at an army post without any evidence before or after of an epidemic prevalence ³⁵ It was not until early November that epidemic disease became obvious These observations covering wide geographic areas at the same time intervals clearly show that influenza does appear in sporadic fashion and it is not an unlikely probability that these episodes represented the stones from which the 1943-44 epidemic was built

It has been observed that epidemics vary quite definitely in their scope and intensity For instance, the outbreak of 1936-37, occurring the world over, was moderately severe and distributed generally throughout the population, while that of 1938 to 1939 represented a mild form recognized largely in institutional groups The same characteristics were observed in other countries that year Hence, influenza A has been shown to change the pattern of its infection widely pandemic, epidemic, endemic or sporadic It is extremely interesting to point out, however, that the form it takes at a given time tends to typify its behavior at widely distant points

The smouldering scattered distribution recently detected with influenza A, seems to be the more common experience with influenza B In most accounts of the past three years there has been reference to influenza B scattering through the population without definite indication of an epidemic unless it be in a limited group ^{32, 33, 34, 35, 44} It has been repeatedly mentioned that many cases of unidentified illness occurred at the same time as the cases of influenza B Observations of the distribution of antibodies to influenza B in the population are in accord with this One series, as yet unpublished, found much lower titers against B than with A but an occasional individual exhibited a high titer suggesting recent infection Nevertheless, influenza B can cause widespread marked epidemics such as were observed in 1936 and 1940 Hence, the pattern in influenza B is also inconstant

The above observations tend to indicate that the influenza viruses are in constant circulation Evidence for human carriers of the viruses is, however, not present Shope has suggested that swine influenza virus represents the 1918 human strain³⁰ and he has observed swine infection with more recent strains of Type A virus⁴⁶ Can swine serve as a reservoir for the human disease? Shope has also presented evidence that

swine influenza virus is maintained in a masked form in the lung worms parasitizing swine from which it erupts when provoking influences disturb the equilibrium⁴⁶ This would account for the storage of virus between epidemics and the explosive manner in which many of them arise The possibility that some similar mechanism serves to preserve the agent in the human body has not been explored Nevertheless, there is ample evidence that influenza can be transmitted from man to man and at the moment this seems to fit best the facts concerning the spread of the disease

EFFORTS TOWARD PREVENTION

The foregoing remarks immediately illustrate certain of the problems which enter into prevention of influenza But it may limit some of the obscurities if we take as a starting point the thesis that the essential requirement of preventive measures is to prevent the virus from reaching the susceptible respiratory epithelium in such a form as to inflict its characteristic injury Studies over several years have shown that the respiratory secretions contain antibodies to influenza virus, apparently derived from the blood, which may represent the most efficient first line of defense since when present they are readily available to the tissues which they bathe^{47 48} They are not constantly present, however, nor are they present in large amounts Nevertheless, it seems that procedures which augment this mechanism may well be effective in procuring protection from the disease It has been found that in recovery from natural infection the protective capacity of the nasal secretions is enhanced but there is as yet inadequate information as to how long immunity persists Indications are that it is much longer than is ordinarily said to be the case, probably for a period of years against the same virus Nevertheless, if infection be induced by a virus so attenuated as to avoid clinical injury it might be applied as needed and build up, through subclinical infection, a relatively durable resistance Certain reports by Bull and Burnet⁴⁹ have yielded results which they considered suggestive but in our studies under a variety of conditions the response to avirulent strains has been too irregular for widespread testing⁵⁰ In one investigation individuals who had developed clinical disease after inhalation of influenza virus, Type B, were subjected to the same procedure with the same virus 4 months later⁵⁰ About one-third again reacted with well marked clinical disease, clearly

indicating that a solid immunity had not persisted for this interval against the amounts of virus employed in the test. The severity of the test is emphasized by the fact that nineteen of twenty-three control individuals came down at the same time. The possibilities along this line have certainly not been exhausted and there are still many reasons for further investigations of immunization by inhalation.

The most widely studied method for attempting to increase immunity has been that of subcutaneous vaccination. It was stated earlier that subcutaneous inoculation of active virus does not produce infection. In animals it can be shown, however, to result in the production of protective antibodies and of resistance. It has been shown also that with proper subcutaneous vaccination the virus-inactivating capacity of the nasal secretions is also enhanced.⁵¹ A number of studies using preparations of virus derived from mouse lung, tissue culture, chick embryo or allantoic fluid have been tested.^{38 41 52 65} In many instances no disease arose to test the result, in others suggestive results have been obtained.

In the winter of 1942-43 under the auspices of the Commission on Influenza, Army Epidemiological Board, 8,000 people in two institutions were included in a vaccination study which employed inactive virus concentrated from allantoic fluid. Studies of the antibody titers before and after vaccination in 419 of the 4,000 vaccinated individuals revealed that over 90 per cent showed a sharp increase in two weeks.⁶⁴ Studies in a smaller group, over a longer period of time, indicated that a slight decline had occurred after 4 months, and at the end of one year the distribution of antibody titers remained well above that before vaccination.⁶

No recognizable epidemic occurred during the winter immediately following vaccination. In an effort to gain information as to what benefit had been attained two groups of approximately 100 individuals each were tested for resistance to infection by intranasal inhalation with Type A and Type B viruses, respectively.

The results indicated that vaccination two to four weeks before infection had a pronounced effect. The influence of vaccination against influenza B⁴¹ appeared to persist during a 4 months' interval while against influenza A this was less evident.⁴⁰

During the epidemic of influenza A which occurred in the winter of 1943-44 the distribution of disease in this population might be con-

strued to indicate a persistence of benefit gained from vaccination a year earlier

On the basis of the experimental studies just detailed an extensive program for the winter of 1943-44 was planned and carried through by members of the Commission on Influenza in an effort to evaluate the effectiveness of vaccination against the natural disease. Results of previous field trials by other investigators suggested that vaccination had a beneficial effect, although the degree of reduction in incidence of disease in vaccinated as compared with control individuals was not sufficiently great to warrant, without further study, the use of this procedure on a wide scale.

The study of last winter, representing the coordinated efforts of members of the Influenza Commission and their associates in six laboratories in different parts of the country, was conducted in A S T P units at eight colleges and universities and in five New York medical and dental schools. Approximately 12,500 men were involved.²⁰

In New York City two studies were organized, one from the laboratories of the International Health Division of the Rockefeller Foundation, by George K. Hirst, Major Norman Plummer and William Friedewald working in the A S T P units at the College of the City of New York, Princeton University and Rutgers University, the other, originating from the laboratories of Cornell Medical College, was carried out at the five New York medical and dental colleges and at Cornell University in Ithaca by Major Norman Plummer, Thomas P. Magill and Wilson G. Smillie. Rickard and his associates carried out a study at the University of Minnesota, Hale at the University of Iowa, Eaton and Meiklejohn at the University of California and a similar program was conducted from our laboratory at the University of Michigan.

The same preparation of vaccine was used by all investigators. Virus for the vaccine was grown in chick embryos and harvested and concentrated from the extra-embryonic fluids. The viruses of influenza A and B were included in the vaccine and were rendered non-infectious by the addition of formalin. Alternate men in each company were given a single, subcutaneous injection of 1 cc. of either the virus vaccine or control material.

In seven of the nine units, the interval between completion of vaccination and onset of the epidemic of influenza A varied from seven to

thirty-one days. In two units, City College of New York and the University of Iowa, vaccination was begun after onset of the outbreak.

The incidence of clinical influenza in the vaccinated group comprising 6,263 men was 2.2 per cent and in the control group of 6,211 the incidence was 7.1 per cent. In almost all localities the trend was the same. Marked deviation from the average result was observed in only one unit where little difference between vaccinated and controls was evident. In the majority of units three to four times as many cases occurred in the controls as in the vaccinated groups. In two units, ratios of five and six to one were recorded. The factors responsible for these variations are not yet understood but may become apparent after analyses of the results are completed.

From the combined results of the study in all units, it would appear that vaccination was effective in reducing the incidence of influenza to about one-fourth, assuming that the incidence of 7.1 per cent observed in the control group was the expected incidence in a normal population. That this assumption may not be justifiable is suggested by observations made in totally unvaccinated companies at the University of Michigan where the incidence of influenza was about 20 per cent to 30 per cent as opposed to 8 per cent to 9 per cent in the control half of the vaccination study groups. If these differences are significant, it suggests that vaccination was of benefit to a proportion of the controls by virtue of their dilution with an equal number of vaccinated men with whom they were in constant association. The effect of vaccination in reducing the incidence of influenza may be greater than is indicated by comparing vaccinated and control subjects in a single homogeneous population. This may be another example of a fundamental epidemiological principle that has found application in the control of diphtheria and other epidemic diseases.

At City College of New York and the University of Iowa, where vaccination was begun while the epidemic was in progress, the morbidity rates were the same in treated and untreated groups, until the end of the first week after vaccination. Thereafter the difference became evident.

At the University of Michigan, during the prevalence of influenza A, an attempt was made to determine the effect of vaccination upon the incidence of the milder forms of respiratory illnesses unaccompanied by fever. All cases with symptoms of respiratory disease reporting to

sick call were studied. Those with temperatures of 100° or more were hospitalized while those who exhibited no significant febrile reactions were seen almost daily in the dispensary until symptoms subsided. The great majority of hospitalized cases was diagnosed as influenza. That a high percentage of these was due to the virus of influenza A was confirmed serologically in about 90 per cent of the unvaccinated group. The afebrile illnesses studied in the dispensary were classified as influenza, local respiratory infection, or cold, depending upon the clinical impression. Except for the absence of significant fever, patients with influenza seen in the dispensary presented essentially the same syndrome as did the hospitalized cases. That the virus of influenza A was etiologically related to the illnesses observed in the majority was demonstrated by appropriate laboratory tests. In the group of cases diagnosed as "local respiratory infections," symptoms were confined to the respiratory tract and there were signs suggesting localized infection, such as sinusitis, pharyngitis, etc. The colds consisted of cases in which the presenting and predominant symptoms were those of rhinitis.

A division between vaccinated and controls within each diagnostic category reveals interesting variations. Of the hospitalized influenzas, the greater proportion were contributed by unvaccinated persons, while of the milder cases, such as ordinarily would not come to the attention of physicians in civilian practice, the differential was less marked. Thus, while the incidence of influenza of all degrees of severity was less in the vaccinated half of the population, in a significant proportion of those in whom infection did occur vaccination appears to have reduced the severity of illness.

The fact that no significant difference is apparent in the incidence of cases diagnosed as local respiratory infections and colds in vaccinated and controls, suggests that the vaccine had a rather specific effect. However, serological study indicates that, during the height of the outbreak, a number of these cases probably were mild infections caused by the influenza virus. It would appear that control and vaccinated individuals contributed equally to the incidence of respiratory illness with the mildest manifestations.

A point of interest noted in all study groups was that the difference in incidence of influenza in treated and control groups was greatest during the height of the outbreak, and as the epidemic subsided the difference between the two became less marked.

Results of this set of studies represent for the first time a clearcut demonstration that vaccination with inactivated virus by the subcutaneous route is capable of protecting to a significant degree against natural epidemics of influenza. They do not indicate, however, that the solution is complete. There is still need for the evaluation of the most effective strains to be employed so as to give the widest range of immunity, there is the question of the optimal amount of virus which can be used, beyond a certain point the possibility of toxic reactions enters, how long does the immunity last and can it be bolstered by multiple rather than single doses, what methods of production of material or even of immunization are to be the most practicable? But above all the problems of technique, it must be kept in mind that it is the production of immunity, not the production of virus, with which we are ultimately concerned. It is also important to bear in mind that the presence of antibodies and immunity are not synonymous, especially in the human individual where a ceiling on antibodies seems to exist.

Passive Immunity The prophylactic approaches which have been discussed are those which tend to induce active immunity by modified infection with active virus or vaccination with inactive material. In both these instances it has been suggested that the effect obtained may reside largely in the influence upon secretions of the respiratory tract. If the superficial cells lining the air passages represent the vulnerable tissues, might it not be possible to protect them by applying immune substances directly at the surface? In other words, the action of the secretions might be augmented by antibodies introduced directly by the respiratory route. Smorodintsev and his associates⁶⁶ were the first to report efforts to study this possibility in the human subject. They subsequently stated that by spraying relatively small amounts of serum which were inhaled by the exposed subject, a marked reduction in the incidence of the disease during an epidemic was obtained.

Studies in experimental animals, largely mice, have repeatedly indicated that serum given intranasally has far greater efficacy than when given by other routes. In spraying for prophylactic purposes, however, it should be noted that excessive amounts of serum over long periods of time have been required to permit any significant results to be observed. On this basis alone one might have certain reservations as to the applicability to the problem of human influenza. In an effort to gain an impression of its usefulness, studies among human volunteers were car-

ried out by members of the Influenza Commission Serum was tested for its capacity to prevent infection by virus sprayed into the nostrils. Details of these studies have not yet been reported but it can be mentioned that substantiation of the statement of the Russian workers was not indicated.

This lecture has touched rather broadly on a wide variety of methods of study which have been employed during the past ten years in the investigations of influenza. It has been seen that knowledge of the viruses, the diseases they produce, and their distribution in nature, have been approached directly. It has become increasingly apparent as well that in order to determine the value of procedures which might serve in the prevention and control of the human disease information must be obtained in human subjects. In this respect somewhat venturesome utilization of the human volunteer has been most profitable, since it permits evaluation of the different proposals in the host concerned. Whether one can consider the experimentally induced infection strictly comparable to the natural disease is not a question, but it does furnish a procedure for investigation. At the moment, the procedure which has given the most definite evidence of limiting susceptibility to influenza has been subcutaneous vaccination. We have indicated, however, that much remains to be done.

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CONCEPTS OF THE IMMUNOLOGY OF
CERTAIN VIRUS INFECTIONS*

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THE concepts which we shall discuss represent the combined efforts of several workers who have been with one of us (P. K. O.) in his laboratory over a period of many years. This work, although carried out in collaboration with different associates** at different times, has a thread of continuity which makes it possible to review it as a whole.

In the early days of virus research, not so many years ago, the facts of immunity were held either as strange or mysterious, or as unaccountable. In the light of investigation the air of mystery cleared and it is now known that serological and immunological processes in virus infections are a counterpart of those characterizing microbic or biological agents. Serum antibody such as agglutinin, precipitin and complement-fixing and neutralizing, can be elicited; the statement that virus infections are followed by a lasting immunity to reinfection has many exceptions—repeated or second attacks of common cold, herpes, influenza, foot-and-mouth disease, phlebotomus fever, poliomyelitis and other virus diseases are recorded—and the dictum that only active virus can induce practical active immunity has had no general application. The serological and immunological phenomena were simply obscured by the nature of the infective agent—its size, non-cultivability *in vitro*, its action as an obligate intracellular parasite, or other factors, but once proper techniques were used, the hidden facts became revealed. At the present time one is not so much concerned with the nature of virus immunology as distinct from that of other biological agents, but rather

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** Their names are in the References at the end of the paper.

with the mechanisms underlying immunity and resistance, or more properly, with those of a host's susceptibility to infection

The general field in which investigations were carried out here is in that of (1) variations in individual host susceptibility which may reflect genetic, maturation or other physiological factors—the so-called “natural resistance”—and (2) individual variations in hosts of uniform primary susceptibility to a virus as studied in experimental animals, the variations being developed either as a result of prior exposure to the virus or of nonspecific factors * The particular problems included the influence of age on susceptibility to infection, the so-called persistence immunity, the correlation between neutralizing antibody and immunity, certain nonspecific factors of resistance, the nature of the virus neutralization test, comparative immunization by means of active and of inactivated viruses, and passive immunization, including its use in therapy

One is immediately impressed with the significance and importance of the knowledge of the pathogenesis of an infection for a profitable study of the principles of immunological phenomena Thus of a malady under investigation, whether naturally occurring or experimentally induced, one should know as far as it is possible, the route by which the virus enters the body, whence it progresses from this point, the tissues in which it then resides or multiplies, the lesions it produces and, after the illness, the way by which the incitant leaves the body, or possibly, how and where it persists For every topic on immunology in each of the following sections here discussed, the importance of pathogenesis is stressed

The first of the subjects is on the variations in individual host susceptibility which are brought about with age

THE INFLUENCE OF INCREASING AGE ON SUSCEPTIBILITY AND ON THE IMMUNE RESPONSE

That age of an animal is a factor in determining the degree of immune response to bacterial and protein antigens has long been known In this laboratory interest was aroused in the problem when it was observed that only infant, but not adult mice succumbed to intraperitoneal injection of vesicular stomatitis virus¹ and again, by the fact that

* Susceptibility or insusceptibility is used in a relative not absolute, sense for the same host can be susceptible to a virus given in the brain but fails to respond when the virus is introduced into the skin The degree to which resistance or immunity is lowered would determine susceptibility, and the degree to which either is raised insusceptibility

young animals of other species also could be attacked by this and by various other neurotropic viruses given by different peripheral routes²

Whatever may be the mechanism underlying the variations in host susceptibility which develops with age, it is of considerable interest. For it is in part the causal factor in producing the differing types of infection, from the inapparent or latent (or perhaps no infection at all on exposure) to fulminating lethal disease. For example, the age factor may be important epidemiologically in influencing the epidemic distribution in certain age groups in a population as occurs in poliomyelitis.

In this laboratory studies were carried out on a development, *pari passu* with increasing age, a) of pre-existing "barriers" in nervous (and non-nervous) tissues, and b) of an enhanced immune response (serum neutralizing antibody plus immunity to a challenge dose of virus).

Barriers The assumption here is that host insusceptibility depends on the changes, not as yet completely defined, developing with increasing age in specific tissues which lie in the path of progression of a specific neurotropic virus. In such tissue virus does not multiply and its progression through and beyond that tissue is thus hindered.

To repeat, knowledge of the precise pathogenesis of the disease induced by the virus under study is essential since the barriers as defined are anatomical. Thus it happens that after peripheral inoculation of young mice, the pathway of the stomatitis virus (determined by histology and by subinoculation of tissue) is in a closed system—axonal, neuronal and trans-synaptic—from the peripheral portal to the central nervous system, attack on the latter leading as a rule to fatal encephalitis. In old mice the virus progresses from the point of entry only to a certain site, the barrier, beyond which the animal is apparently unaffected, it therefore survives without showing signs of disease. After intracerebral inoculation of the virus in young or old mice, however, the virus is placed on the other side of the barrier, into susceptible tissue, then it progresses widely and at random throughout the CNS.

In this way the pathogenesis of the disease and the spread of virus from periphery to CNS for different species of animals and of viruses were determined^{3,8} and the sites of the barriers mapped. The latter in resistant, older mice were located after intraocular exposure, in the retina, after intramuscular, the muscle or myoneural junction, and after intranasal instillation, the anterior olfactory area of the brain. In old guinea pigs after intramuscular or pad inoculation, the site was found

at the myoneural junction or specialized nerve endings and after intranasal instillation, between the nasal mucosa and the olfactory bulbs. For Eastern and Western equine viruses in resistant older mice and guinea pigs the barrier was located in the blood vessels.^{4,8}

What are the grounds for the concept that adult tissue—the barrier—does not support multiplication of virus, rather than that the virus is stopped in its pathway owing to a generalized immune response? It was shown that vesicular stomatitis virus injected intramuscularly in young mice multiplies actively in the muscles, in old ones no such local multiplication occurs and even though virus persists there it invades neither the sciatic nerve nor the CNS—the pathway of the virus in the young.³ It is of interest, however, that although old mice are insusceptible to intramuscular inoculation they are still susceptible when the muscle barrier is surmounted by introducing virus into the sciatic nerve whence it progresses to the CNS bringing about fatal ascending myelitis and encephalitis. Again, lack of any appreciable quantity of circulating virus in intraperitoneally injected adults⁹ (when viremia is the rule in the young) may be linked with the insusceptibility of peritoneum, since the adult CNS is fully susceptible to infection. Moreover, young, actively multiplying (metabolizing²) tissue is generally more responsive to many viruses and also to tumors (Rivers, Friedewald and Kidd). Also, chick embryos are readily infected by many viruses in contrast to chicks after hatching which become insusceptible to the same incitants.¹ One can conclude, therefore, that with age non-nervous tissue—the “peripheral organism”—becomes increasingly resistant to virus.

Immune Response Seen from another view⁹ age is a factor in determining in the experimental animal its immune response (production of neutralizing antibody plus immunity to a challenge dose of virus). Even though young and old are equally susceptible to equine encephalomyelitis virus introduced into nervous tissue,¹⁰ the response of infant mice to immunization with active or with inactivated virus is slow and feeble, of older ones, rapid and strong, when the challenge dose of virus is introduced extraneurally. The difference in response may account therefore for the increasing insusceptibility to infection developing with age.

THE CORRELATION OF ANTIBODY WITH IMMUNITY TO REINFECTION

In an elaboration on the role of neutralizing antibody in experi-

mental equine virus infection it was found⁹ that during active immunization much less antibody is correlated with immunity to peripheral than to intracerebral administration of a challenge dose of virus. The difference in pathogenesis of the infection progressing from these two sites of injection should^{4,5,6} be borne in mind. As described, after peripheral inoculation into normal young mice the virus reaches the CNS via the blood, into vaccinated ones, no virus is detected in the blood—it is neutralized before it can get to the susceptible CNS tissue, after intracerebral inoculation, virus is placed in direct contact with susceptible tissue and the antibody in the blood is therefore of no immediate significance. One can therefore picture the susceptible cell in the CNS as being bathed not by the circulating blood but by interstitial fluid, that its protection would depend on the concentration of neutralizing antibody in this fluid or, in other words, on the availability of antibody to the cell.¹¹⁻¹³ The following elucidates this point.

It was shown¹¹⁻¹³ that the neutralizing capacity of serum and of spinal fluid of rabbits vaccinated with equine virus paralleled each other at a ratio of the order of 300:1—just as has been reported for a bacterial antigen by Freund. That is, when serum dilution of about 1:300 or higher neutralizes virus one can then expect the spinal fluid (also blood-free brain tissue) of a rabbit to contain demonstrable antibody and the animal can then survive an intracerebral test inoculation of large doses. When, however, this serum titer is not reached, no antibody is detectable in the spinal fluid and the rabbit succumbs to infection. The results would suggest therefore that the immunity of the CNS is dependent on the concentration of antibody available to that particular tissue (cf. Fox, in yellow fever of mice).

The factor of availability of antibody to particular tissues applies, of course, to other viruses as well. In foot-and-mouth disease¹⁴ large doses of antiserum given subcutaneously fail to arrest vesicle formation at the site of plantar inoculation of virus but a certain amount of serum, depending on its potency, prevents generalization of lesions (Waldmann and Pape, cf. also Francis' work on influenza). In such animals in which a high level of antibody is induced by means of formalized vaccines, even the local lesions can be prevented (Bedson et al.).

In a practical sense the studies on the correlation of antibody to immunity offer an indicator of the possible effectiveness of a vaccine: an adequate level of induced serum antibody is associated with immun-

ity to infection by peripheral route¹² The goal in vaccination would therefore be production of a proper level of serum antibody

THE NEUTRALIZATION TEST

By means of a neutralization test one can determine the presence either of a virus or its specific antibody depending on which of the materials is designated the unknown It is usually performed by adding fluid containing suspected antibody to suspensions harboring virus and after varying periods of contact injecting the mixture, properly controlled, by a specified route

It is an important test for it is used ordinarily to detect the prevalence of a disease, or the geographical dissemination of a virus or as a method of immunological study It is therefore natural to seek out the variables of the test, to increase its delicacy and its precision and to study its mechanism

Earlier observers maintained that the correlation, mentioned in the preceding section, between serum neutralizing capacity and the degree of immunity, did not exist

The neutralization test is ordinarily carried out using undiluted serum plus virus dilution In certain circumstances it is important to employ serum dilutions plus a constant amount of virus in order to reveal the true picture By means of the described "dilution" tests^{9, 11 13, 15, 16} a correlation can be deduced between the neutralizing capacity of serum antibody and immunity to test doses given either by way of the brain or extraneurally

It was furthermore demonstrated¹⁷ that a difference exists in the protective capacities of antisera to the equine viruses which depends on the route of injection of mixtures, for example, whether in mice the route is cerebral or peripheral (peritoneal, muscular) The former method shows 100 or even 10,000 times less neutralizing capacity than the latter, "peripheral," procedure with the identical test materials Studies are now being carried out which point to the availability of complement in the local, extraneural, tissues for completion of neutralization as one of the mechanisms possibly underlying the enhanced peripheral neutralization^{18, 19}

The neutralizing capacity of a given antiserum to the Western equine virus varies also according to other conditions of the test, as for example, use of fresh, frozen, stored or heated serum and incubation

of serum-virus mixtures before injection. To conclude from the results of extensive investigations,^{18,20} it would seem that complement or a virus-inhibiting factor, plays at least some part in the neutralization of the equine virus by its antiserum, just as either may be the key to the solution of the problem of greater capacity for virus neutralization by certain routes of injection. What particular substance may be involved is still under study and present investigations include connection of virus-inhibiting substance not only with serum-virus relationships but also with immunity in general.*

ACTIVE AND PASSIVE IMMUNIZATION

Immunization with Active and Inactivated Viruses The virus of equine encephalomyelitis, inactivated especially by means of formalin and in sufficient dosage can reproduce the antigenicity of active virus, as shown by the development of neutralizing antibody and by resistance to test inoculation of virus.^{15,16} For example, mice vaccinated with formalized virus develop at 2 weeks fully as high a concentration of serum neutralizing antibody as do mice vaccinated with active virus. The concentration falls in both groups during the following 6 months and at the end of that time is increased markedly by a single dose of active or inactivated virus. So also a similar curve can be shown for the immunity developing to test doses of virus introduced into the brain. Moreover, an immunity can be induced in mice and guinea pigs with vaccines in which no infective agent could be demonstrated by tests made as rigid as possible.²² Elaborate tests were made, for the absence of multiplying virus is a crucial point in the problem of "persistence" immunity to be discussed later. Can a minute amount of active virus (less than one infective unit) residual in a vaccine and escaping detection, immunize an animal? It was found by test that^{17,22} such an amount is ineffective, indeed, a relatively large dose of active virus is needed for successful immunization of normal animals.

Another point of practical significance is that vaccines, to be potent for immunization, should contain a high concentration of virus before inactivation.²² For the equine virus, the potency of vaccines depends on its use in undiluted state, the immunizing power falls even to its complete extinction when it is diluted 1:10 or higher. The lack of

* An interesting development during these studies was that the equine virus antibody was recovered after electrophoresis, from the gamma globulin and from the albumin of rabbit antiserum.²¹

sufficient quantity of antigen may also be one of the reasons for the difficulty of immunization with poliomyelitis virus²³

Still another practical development is in the use of mouse brain as a source of the equine virus vaccine. It was pointed out²⁴ that it can replace to advantage infected horse brain which was first used by Shahan and Giltner. Intensive study revealed its effectiveness although chick embryo vaccines have in time supplemented other preparations chiefly for practical reasons (expense and ease of preparation). At present mouse brain vaccines have been recommended for preventive use in experimental St. Louis and Japanese B encephalitis and in man in Russian tickborne encephalitis.

Finally, instead of formalin as an inactivating agent for preparation of antigens for immunization or other purposes, ultraviolet radiation can be used²⁵. The antigenicity of such virus rapidly diminishes, however, with further irradiation—an effect which stands in the way of its practical use, an objection applying also to certain other viruses.

With respect to immunization with active virus, early investigations (1925-1928) have indicated that for vesicular stomatitis virus²⁶ and for foot-and-mouth disease virus,¹⁴ injection into the skin in sites other than the pads of the feet of guinea pigs (in which the viruses cause local vesicular lesions) is followed by an absence of any visible local lesion or of any objectively obvious sign of illness. Yet the viruses become generalized through the circulation and induce after a single sufficient dose a high degree of immunity to reinoculation in the pads (v. supra). It was later found by others that this method can be applied in prevention of certain other virus maladies.*

Passive Immunity. Of the more practical studies in this field as carried out here and to be discussed now are a) blocking effect of antiserum on antigenicity of active and inactivated virus, b) use of antiserum in nasal seroprophylaxis and c) experimental serotherapy.

Investigations on the effect of immune serum on the antigenicity of active and inactivated equine virus demonstrated that the antigenicity of both can be blocked and to the same extent by adequate amount of antiserum²⁸. A discussion of the rationale will be passed by, but this can be stressed: the failure of vaccines to bring about immunity when

* By constant association with active equine virus over long periods of time serum neutralizing antibody may be produced to an appreciable degree as occurred in a laboratory worker exposed to the virus for about 6 years²⁷. Such probable inapparent infections followed by production of antibody have been shown later to arise not infrequently in areas where the virus is disseminated and its vector abounds (Howitt-Hammon).

they are injected along with, or some short time after antiserum—a procedure used now and again in practice—is based on this blocking effect

Nasal instillation of antiserum as a preventive of infection was studied with viruses progressing along the nasal pathway, and it was shown²⁹ that the method was effective to a certain degree against experimental pseudorabies and Eastern equine virus infections. When antiserum was instilled as a single dose intranasally in guinea pigs, they were protected against lethal infection with the viruses given by way of the nose. The protection was evident from the time of serum instillation until at least 5 but not 24 hours later. This type of passive immunization has recently received renewed impetus from the work of Professor Smorodintsev of Moscow and his colleagues on similar successful prevention of influenza in man. The rationale of the preventive effect may lie in the fact that a sufficient amount of neutralizing antibody is made available locally to susceptible tissues or at the portal of virus entry.

Serotherapy of experimental Western equine virus infection in guinea pigs is effective if antiserum is given in single or multiple doses 24-48 hours after virus inoculation (cf. Zichis and Shaughnessy), it is ineffective if treatment is begun after onset of definite signs of encephalitis. It would thus seem, if sufficient antiserum can be administered in such instances as in laboratory infections in which exposure to virus can be ascertained and even prodromal signs noted, that a hopeful outcome may be expected in an otherwise highly fatal infection.³⁰

An interesting side effect was observed during the tests on serotherapy. Several serum-treated animals developed encephalitis after unusually prolonged incubation periods (13 to 47 days). The "delayed reactions" arose when serum-antibody had fallen to a low titer but was still demonstrable. The virus probably persisted in the CNS throughout this long period since it could be neutralized by serum-antibody if it progressed from an extraneural portal to the CNS. The delayed reaction, which further limits the use of serotherapy, occurs therefore when a low serum antibody titer is reached, when antibody content of the CNS becomes ineffective to prevent virus from passing to and infecting other cells.³⁰

"PERSISTENCE IMMUNITY"

An exciting hypothesis to account for the enduring immunity which follows certain virus infections is that it is correlated with the per-

sistence of virus in the host tissues, commonly called "persistence immunity" If the correlation is to stand, the negative must be true the host becomes susceptible to infection once the virus leaves him The proposition, stated perhaps for the first time in 1887 by L. Pfeiffer, who suggested chiefly on the basis of clinical observation that a man is immune to smallpox as long as he carries the virus, has been the subject for study in this laboratory for many years

Among the many reasons offered for accepting the hypothesis are several cogent ones (1) Virus neutralizing antibody has been shown to persist for a life time in certain infections characterized by lasting immunity Sawyer states that serum antibody was found 75 or 78 years after an attack of yellow fever Since antibody is produced as a reaction to specific antigen (virus) it is assumed that the latter must be present all that time to offer the stimulus although Sawyer declares that with time the antibody may in exceptional instances become undetectable and it is unknown whether "immunity could ever fall so far as to permit a second attack of yellow fever" In other words, tissue immunity to reinfection may be a more sensitive test of the immune state than is circulating, neutralizing antibody^{9,31} (2) For those infections followed by a temporary immunity, the proponents of the persistence hypothesis postulate that the virus attacks, and may persist in susceptible tissue that is superficial and is thus shed, along with the contained virus, within a short time—as possibly in influenza and common colds (3) Immunization with active virus produces generally durable and solid immunity (4) In such experiments carried out in immune hosts in whom search for virus failed, it is assumed that the failure offers no evidence that the host is virus free, only that the proper experimental procedure is not or cannot be applied (5) Virus can persist in immune carriers even though they possess a good amount of neutralizing antibody, it is conjectured that the virus resides within the host's cells If so this intracellular position affords the virus protection from the antibody (Rous and Jones and others) (6) A significant test with a plant virus as reported by Kunkel is contributory evidence for persistence immunity The yellows virus can be inactivated at 38-42°C maintained for 2 weeks, which spares the plant (here the periwinkle) The cured plant can then be re-infected, as if it were normal, it can thus be infected and cured as often as desired

Are all the correlations as just stated in this relatively simple propo-

sition of enduring immunity being dependent on persistence of virus, purely accidental or fortuitous as some would believe?

In early experiments³² vaccine virus was recovered from the tissues of an immune rabbit 114 days after inoculation of virus. Later Dresel showed that in similarly tested rabbits virus was recoverable up to but not beyond 8 months after inoculation, although immunity endured at least a year. The subject was studied here anew³³ and it was found that the immune state (i.e. presence of agglutinin and neutralizing antibody plus immunity to reinoculation of virus) was evident 2 or 3 years after infection, at a time when the animals were showing signs of old age. But no virus could then be detected. Vaccinal immunity therefore lasted beyond the persistence of recoverable virus. It should be stressed that the absence may also mean that the quantity of virus is so reduced in the tissues that a single infective unit is difficult to isolate. Moreover, not all tissues were tested, and finally, the virus if masked by antibody would be undetectable by the available methods.

Virus has also been obtained in well and presumably immune animals within about 3-4 weeks of convalescence from experimental infection (foot-and-mouth disease,¹⁴ poliomyelitis in the monkey³⁴). These positive results were however exceptional: in foot-and-mouth disease 20 additional cattle examined 20-176 days after experimental infection were negative¹⁴ and in poliomyelitis, additional studies³⁵ showed that the virus rapidly disappeared (within a few hours) from the tissues of immune animals. Again, in recent tests with the Western equine virus,^{36, 38} the latter was found at 28 but not at 72 hours in the CNS after its injection into immunized animals.

Furthermore, as opposed to the hypothesis, and placed against item 3 cited above (active virus injection produces solid and durable immunity) are the results of recent experiments^{16, 22} revealing that animals can be immunized by a sufficient dosage of formalin-inactivated equine virus to at least as high a degree of immunity as that induced by active virus. It is yet to be shown that the immunity following inoculation of active virus can generally equal that following an attack of the disease itself. Practical immunization can therefore be achieved by means of inactivated virus.^{12, 16, 22, 25 *}

* In this connection, the striking results of Chase should be cited: a chemical antigen (2,4-dinitrochlorobenzene) can induce a satisfactory level of cutaneous hypersensitiveness enduring for at least 7 months after a series of treatment attempts to recover antigen from the animals failed (personal communication). Sulzberger, who publishes instances of persistence of antibody for several years in persons not exposed again to the antigen, states that "persistence of living microorganisms is not necessary to account for the continued state of cutaneous or other allergy (including the persistence of immunity to reinfection)".

In favor of persistence immunity is the possibility that virus in immune hosts may be masked by neutralizing antibody and therefore is not recoverable by ordinary methods. If this obstacle can be surmounted and if, in addition, the work by Kunkel on plants can be made to apply to mammals, one will be in a better position to affirm the hypothesis. In conclusion, no definite evidence was obtained by the methods thus far used to support the idea of immunity based on persistence of virus.

THE RESPONSE OF THE IMMUNE ANIMAL TO A CHALLENGE DOSE OF VIRUS

Animals (rabbits, guinea pigs, and mice) sufficiently vaccinated with the equine virus exhibit immunity to large test doses of the homologous virus introduced intracerebrally but full susceptibility to the heterologous strain.*

Rabbits or guinea pigs adequately vaccinated to withstand 1000 lethal cerebral doses respond to challenge dose with a characteristic febrile reaction. In vaccinated or nonvaccinated animals the febrile response, a steep rise in temperature first observed 2 hours after inoculation which persists for 24-30 hours, is similar. Thereafter, fever continues in control animals until prostration but in immune ones the temperature drops to normal where it remains.

Since no such characteristic rise in temperature occurs in guinea pigs or rabbits after intracerebral injection of formalin-inactivated virus, or of suspensions of normal mouse cerebral tissue, or of a neutral mixture of virus and antiserum, and since the virus is recovered from the perfused brain of guinea pigs during the febrile period, it is plain that the fever in vaccinated animals reflects virus action and therefore an abortive infection.^{87,88}

The confirmation of the phenomenon as an infection was obtained by histological study and by demonstration of fluctuations in the neutralizing antibody in the brain tissue. The cerebral lesions in vaccinated animals were comparable in type and, with few exceptions, in degree with those in nonvaccinated ones, as observed 24-48 hours after virus inoculation. It is noteworthy that vaccinated animals, presumably immune at the time of introduction of the challenge dose do not rid them-

* Two strains of equine encephalomyelitis virus exist in nature the Eastern and the Western. Both are serologically and immunologically distinct, i.e. there is no cross neutralization nor cross-immunity in animals recovered from infection or vaccinated with either active or inactivated virus.

selves of the equine virus immediately after exposure, before any damage is done. On the contrary, immune animals permit invasion by the virus, allow its persistence (even though for a short time—here, a day or two), and exhibit during earliest stages definite pathological changes of the same type* and practically of the same degree as those seen in non-immunes. The virus progresses in the latter in its destructive course of necrosis of neurons, of stroma of the CNS, and of vascular walls until the ultimate death of the host. In immunes it acts to gain in the brain only a foothold—actual multiplication of virus cannot be demonstrated—when it meets certain obstacles, the defensive mechanisms, which, as it were, stop it in its tracks. Then it is undetectable, nevertheless, first leaving its impression on the brain in certain lesions which reflect abortive infection. Bedson earlier observed a similar condition in experimental psittacosis. Vaccinated, immune mice after test inoculation with virus show no signs of disease, but definite, characteristic lesions in the spleen, in which active virus can be found. The production of lesions—a consequence of the effects of virus—is therefore evidence for an actual infection.

Still other evidence for infection is the variation in “brain” antibody “serum” antibody ratio. Thus during the febrile period no change occurred in the ratio over that prior to the test virus inoculation. One week after the test dose was given, however, brain antibody rose considerably so that the ratio shifted from about 1:300 to 1:1 or 1:10, the second week after, it returned to about 1:100. How can this be viewed? In an immunized animal, after a test dose is given intracerebrally, an excess of the virus is deposited in a site containing antibody, virus remains in excess for about 24-30 hours, then follows an excess of antibody, in this way the animal overcomes its infection and remains well.³⁸

To summarize the ideal state in immunization by artificial means with active or inactivated virus, that is, one in which the host after any sort of exposure to virus promptly and completely sheds or eliminates any dosage of it is not readily achievable. When an adequate

* Examination of the CNS of stock animals and animals after vaccination revealed no visible changes. Other material such as formalized virus or normal guinea pig brain, inoculated intracerebrally, gave rise to lesions in the same elements as were involved in the earliest stages within 24-48 hours of infection with active virus. Slight cellular infiltration chiefly with polymorphonuclear cells in meningeal and perivascular areas, and mild disorganization of lining cells accompanied by similar cellular infiltration of the ependyma and choroid plexuses. Whether the changes are induced by cortical hemorrhages—almost invariably concomitants of the inoculation—or by the inoculum itself is not known. The degree of this reaction therefore differentiates it from that caused by virus. Not all viruses respond in this way, for example our finding for herpes³⁹ later confirmed by others for poliomyelitis virus, herpes virus can multiply in guinea pigs' brains without evoking any distinctive signs of disease or histopathological lesions.

amount of equine virus is given it will gain a temporary foothold in the vaccinated, apparently highly immunized, animals even causing certain changes which may be reflected as an abortive, or possibly an inapparent infection

NONSPECIFIC RESISTANCE * INTERFERENCE PHENOMENON

Since the living cell is needed for the multiplication of viruses, its condition is necessarily linked with the fate of the latter. One type of nonspecific resistance may result from an alteration of the normal cell by (1) specific virus action or (2) general disturbance of metabolism as in malnutrition. Another type of nonspecific resistance may be due to (3) mechanical factors influencing the progression of a virus from its portal of entry.

1 *Interference due to virus action on cells* When a tissue harboring a virus is exposed within a definite time to another virus, or when two viruses are injected at the same time, and one inhibits the multiplication or modifies the action of the other, the process involved, which is not dependent on neutralizing antibody or on serological specificity, is designated the interference phenomenon. The interest of this laboratory in the problem concerned additional examples of this reaction, particularly in the CNS tissues, the classification of viruses on the basis of their "interfering" capacity and studies of the principles involved in production of the resistance.

Rabbits or guinea pigs convalescent from experimental Eastern or Western equine virus infection induced by intracerebral inoculation withstand, during a period of two weeks, similar injection of both viruses, also of that of vesicular stomatitis^{37 38}. This resistance is not brought about by introduction into the brain of subinfective amounts of active or formalin-inactivated virus, nor does it depend on neutralizing antibody in the circulation or brain. The resistance is confined to the CNS because heterologous virus after peripheral inoculation is not prevented from circulating in the blood stream. One virus given in the brain interferes therefore with another given in the brain. Moreover a small dose of Theiler's virus (mouse poliomyelitis⁴⁰) introduced intracerebrally into mice and giving rise to incubation periods of 6 to 14 days induces from the fourth to the tenth day, an increasing resistance

* To be noted is that reference is made to 'immunity' when specific antibody or the general principles of specificity are involved, to 'resistance' as now used in this section when non specific factors are dealt with.

to large doses of Western equine virus given intracerebrally. Not only does the Theiler virus interfere in mice with Western virus but also with Eastern and certain other neurotropic viruses—the tests are still being carried on^{37,38}. From what has been said, one should hesitate to use animals recently tested, as is done in laboratory identification of newly isolated viruses or strains for fear of encountering this nonspecific phenomenon.

2 *Interference due to general disturbance of metabolism* It was first shown experimentally by Rous (1911) for the Rous sarcoma and in this laboratory (1925) for a virus such as foot-and-mouth disease⁴¹ that thin, marasmic, or ill-nourished animals are resistant to inoculation,* moreover, the resistance is nonspecific—it is not evoked through the action of neutralizing antibody⁴¹. Rivers and colleagues have also demonstrated that rabbit skin irradiated with ultraviolet light is less susceptible to vaccine virus than untreated skin.

Nasal chemoprophylaxis Another form of nonspecific resistance studied here is that following nasal instillation of certain chemicals (tannic acid, alum, zinc sulphate as used by Schultz, etc.) to prevent viruses which progress along the olfactory pathway from reaching the CNS.

The chemoprophylaxis, as described, was first observed in 1934 in experimental equine encephalomyelitis,⁴² it was promptly applied to various viruses including experimental poliomyelitis,^{43,44} in the latter case it was 100 per cent effective. When, however, it was applied to human beings during an epidemic of the malady, the method failed for the reason, as now believed, that the virus is in nature not ordinarily transmitted via the olfactory pathway.

The mechanism underlying the action of nasal chemoprophylaxis is still being studied, although it was thought that the chemicals sprayed or instilled into the nasal cavity damaged in some way the olfactory mucosa (neurons), thus preventing infection by the virus, restored susceptibility followed the restitution of the membrane (Schultz and Gebhardt).

3 *Interference due to mechanical factors* Nonspecific resistance is not always due to cellular changes but can arise from mechanical factors such as blocking the progression of virus from its portal (King, Sprunt and colleagues). In this laboratory⁴⁵ it was shown that following the use of hypertonic solutions producing edema, a virus such as

* Cf. the dictum of Rivers: "Perfect health is no protection against poliomyelitis!"

herpes febrilis progressed more actively with an enhancement of obvious signs of infection. On the other hand, substances inducing acute inflammation and partial or total blockade of the lymphatic system, retarded or even inhibited virus infection.

In summarizing the theoretical aspects of the problem of interference, especially that due to virus action which is designated in this laboratory as "an acquired nonspecific cellular resistance,"³⁷ one should draw attention to the susceptibility of normal cells and the resistance of "abnormal" ones to virus. Just what the mechanism of resistance is is still unknown. One view is that virus affects the receptor or receptor substance of susceptible cells thus inactivating it (after Hirst who postulates this to be the mechanism of hemagglutination by influenza virus). If any one virus interferes with any other, the phenomenon then is completely nonspecific—cells made "abnormal" through virus action become refractory to infection by another. If, on the other hand, only specific cell receptors are inactivated, without otherwise affecting the normality of the susceptible cell, it may then maintain the "interfering" power of virus. In such an event one can conjecture on the possibility of prophylaxis, after the manner of chemoprophylaxis, further study may show the way.

At this moment the insusceptibility of a host to infection depends on a number of factors, perhaps more than one acting concomitantly. In experimental equine encephalomyelitis, certain of these factors are, first, the *systemic strain-specific immunity* in which the degree is correlated with the titer of neutralizing antibody, and can be active, as (a) in recovery from disease or from inapparent infection, (b) after vaccination, or (c) in the anamnestic state consequent to recovery, vaccination, or exposure to active virus) or passive (as from maternal transfer of antibody or from injection of antiserum). The second factor is *cellular resistance* independent of neutralizing or other specific serological antibody and is nonspecific, developed through virus action or through cellular changes (nutritional, endocrinological, genetic) not induced by a virus. Another form of nonspecific resistance is due to *mechanical factors preventing progression of a virus* from its portal. Still another is *maturation*—the increasing insusceptibility with age which is correlated with increasing capacity to produce virus antibody, or with cellular changes ("barriers") or with both. This is an instance in which time has not served to simplify nature!

One word before closing this lecture. The whole story is not told, yet the speakers must save themselves from the quicksands of illusion, they must give no other impression than that their colleagues and themselves are at the very threshold of knowledge of the subjects here discussed.

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DIFFERENCES IN THE NATURE OF ANTIBACTERIAL ACTION OF THE SULFONAMIDES AND PENICILLIN AND THEIR RELATION TO THERAPY*

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THE therapeutic effectiveness of the sulfonamide drugs is due solely, insofar as can be determined, to their bacteriostatic property—the ability to restrain the growth of the organisms. They do not exert a primary killing effect. The killing of the infectious agent is left to the normal body mechanisms, apparently chiefly through phagocytosis which occurs most actively when specific antibody is present, whether because of active immunization of the host by the infectious agent during the course of the disease itself or else supplied artificially through the use of immune sera—a procedure which many consider to be seldom necessary nowadays except in the case of bacteria which produce exotoxins, such as the gas gangrene anaerobes. Dependence on specific immunity is thus an important limitation to the effectiveness of the sulfonamides, since, unless phagocytosis is active the infectious agent may not be eradicated. A more ideal chemotherapeutic drug is one which will kill the microorganisms without such complete dependence on the complex antibody-complement-phagocyte system. There are indications that in the animal and human body penicillin exerts this effect to a considerable degree and its greater usefulness in many cases may be due to its killing or bactericidal property.

It seems proper to review certain parts of the evidence on which the foregoing observations with respect to sulfonamides and penicillin are based. In the case of the sulfonamides this can be very clearly dem-

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onstrated by a consideration of the therapy of experimental pneumococcal infections of mice¹

If mice are infected with pneumococcus Type I and treated with a sulfonamide such as sulfapyridine or sulfadiazine, therapy must be continued for a period of 48 to 72 hours for recovery to take place. The same amount of drug given on a single day is ineffective. Experimentally, in other groups of mice, it can be shown that a period of 60 to 72 hours is required for the development of active immunity. Pneumococcus Type I is a good antigen so that between 90 and 100 per cent of mice become immune during this period. The sulfonamides are very highly effective against infections with Type I and uniformly, between 90 and 100 per cent of infected mice recover following treatment for three days. In other words, the proportion of animals recovering following sulfonamide therapy corresponds closely to the proportion of mice which becomes immunized by a single injection of killed Type I pneumococci.

In the case of pneumococcus Type III the story is similar but at the other end of the scale. Although most strains are as susceptible as Type I to the bacteriostatic action of the sulfonamides *in vitro*, in experimental infections of mice these compounds are relatively ineffective. Between 5 and 10 per cent only of mice infected with Type III pneumococcus recover following sulfonamide therapy continued for as long as five days. During the period of drug administration the animals remain well, but when the drug is stopped most of the mice die. In other words, the drug has exerted a bacteriostatic effect, but due to some failure on the part of the host, destruction of the bacteria has not occurred. There is evidence that this failure is due to the inability of the host to produce antibodies to pneumococcus Type III, except in a small proportion of cases. Pneumococcus Type III, relatively speaking, is a poor antigen. If groups of mice are injected with a heat-killed vaccine of this organism, only 5 to 15 per cent develop active immunity against even a very small dose of living organisms. The proportion of animals which survive following sulfonamide therapy is about the same as that which becomes immunized to pneumococcus Type III when injected with a heat-killed vaccine.

Admittedly this is not hard and fast evidence that in strains of organisms of equal virulence and *in vitro* susceptibility, the difference in effectiveness of the sulfonamides in curing infections with these bac-

TABLE I

RELATION OF THE EFFICACY OF SULFONAMIDES TO
ANTIGENIC RESPONSE OF MICE TO PNEUMOCOCCI

<i>Pneumococcal Type</i>	<i>% surviving following sulfonamide therapy</i>	<i>% immunized by heat-killed vaccine</i>
Type I	90-100	90-100
Type II	50-60	50-60
Type III	irregular 0-10	5-10

Virulence of all strains for mice 10^{-8} cc of culture

Susceptibility of strains to bacteriostatic action of sulfonamides *in vitro* the same within the limits of error of test

teria is due to differences in the immune response of animals to them. Further evidence that the immune response is of primary importance may be got from a study of infections with Type II pneumococcus. In its response to the sulfonamides in experimental infections, Type II lies midway between Type I and Type III. The sulfonamides will effect cure of approximately half of the mice infected with Type II. Correspondingly, if one injects mice with a single dose of a heat-killed vaccine of Type II pneumococcus, it is found that only about half of the animals develop immunity. The evidence would appear to be quite clear therefore, that in experimental infections of mice with different strains of pneumococci of the same virulence and *in vitro* susceptibility to sulfonamides, but differing in their antigenic potency, the therapeutic effect of the drugs is directly proportional to their antigenicity. A summary of these observations is given in Table I. From these data it can be seen that the effectiveness of the drugs parallels the antigenicity of the bacteria to a remarkable degree.

The antigenicity of these three types of pneumococci in other animals including man, parallels roughly that observed in mice, with Type I an excellent antigen and Type III relatively poor. It is also of considerable interest that in man, infections with Type III pneumococcus respond to sulfonamide therapy less well than infection due to other types. The overall mortality in pneumococcal pneumonia treated with sulfonamides is in the neighborhood of 10 per cent, whereas with

Type III the mortality is between 20 and 25 per cent

Failure of action of sulfonamides in localized infections For a time it was thought that sulfonamide inhibitors were solely responsible for the failure of sulfonamide therapy in certain localized infections such as empyema. Extensive study of experimental pneumococcal empyema in rabbits² indicates, however, that this is not uniformly so, since in some instances relatively enormous doses of sulfadiazine injected locally failed to sterilize the cavity even though we were unable to detect the presence of any sulfonamide inhibitor whatsoever, and the reaction of the pleural exudate was neutral or slightly alkaline. Factors other than these must then be sought in order to explain the lack of effect. It should be noted that the organisms used to produce the empyema remained highly susceptible to the bacteriostatic action of the drugs *in vitro*. The reasons for failure of the sulfonamides locally may be that antibody in sufficient quantity does not enter the lesion and that most of the leukocytes in the exudate are dead or damaged and no longer actively phagocytic. Absence of antibodies and functional phagocytes has seemed to us to be the most probable explanation, since, although a bacteriostatic concentration of sulfadiazine could be achieved in the absence of demonstrable inhibitors, the organisms were not destroyed. This is further evidence for the importance of the normal host defense mechanisms in the action of the sulfonamides. It is apparent that the purely bacteriostatic action of the sulfonamides and lack of a bactericidal effect place serious limitations on their usefulness.

Bactericidal action of penicillin Penicillin has changed entirely our approach to the therapy of local infections such as empyema. Not only does it sterilize a pneumococcal empyema cavity, but this effect may occur within 4 to 8 hours. This is true both in experimental animals and in man. It seems most likely that the dramatic response to penicillin injected locally under such circumstances is due to the direct bactericidal action on the organisms as opposed to the bacteriostatic effect of the sulfonamides, which requires to be supplemented by antibody and phagocytes.

Hobby, Meyer and Chafee³ demonstrated that penicillin exerts a bactericidal effect *in vitro* and this observation has been confirmed repeatedly by others. Killing does not occur instantaneously as when a culture of bacteria is dipped into boiling water, nonetheless the effect is quite definite. It should be noted, however, that usually not all of the

organisms are killed *in vitro*, a few remaining alive

When penicillin is injected locally into empyema cavities, the bactericidal effect is even more striking than that which occurs *in vitro*, provided one is dealing with penicillin-sensitive organisms. What evidence is there for a bactericidal effect in infections other than empyema?

In patients treated for anterior urethritis by intramuscular or intravenous injection of penicillin, it has been noted that viable gonococci may disappear within a few hours. Similarly, spirochetes may disappear from a primary chancre within a matter of a few hours following initiation of treatment. Both of these observations indicate that penicillin is exerting a direct killing effect on the infecting microorganisms. On the other hand, in the case of anterior urethritis treated successfully with a sulfonamide, similar dramatic disappearance of the gonococci does not occur, but may take several days. It may be argued, however, that this does not rule out specific immunity in the case of penicillin therapy, since by the time treatment is begun the microorganisms have been present in the body for a sufficient period to provoke a specific immune response. This would be true even if chemotherapy is begun on the first day of clinical disease since the organisms have already been present during the incubation period which might provide sufficient time for the production of immune bodies, although the amount might be very small and not detectable by the methods available. In this regard it has been shown in rabbits that active immunity in the case of pneumococci appears before specific antibodies are demonstrable in the circulating blood.⁴

The lesser role played by specific antibody in penicillin-treated infections is demonstrated by experiments in mice infected with pneumococci and treated with penicillin.

If mice are infected with pneumococcus Type I and treated with penicillin in three divided doses at 4 hour intervals thereafter on the day of infection only, a considerable proportion of the animals survive. Under this scheme the last dose of penicillin is given 8 hours after the animals were infected. The recovery rate depends in good part upon the amount of penicillin injected and reaches a figure of approximately 75 per cent when large amounts are given. It seems unlikely that an effective concentration of drug is present in the animal body for more than 12-16 hours after the infection was initiated, yet during this period penicillin has been able to eradicate the infection completely from most

TABLE II

EFFECT OF PENICILLIN GIVEN ON A SINGLE DAY TO MICE
INFECTED WITH PNEUMOCOCCI

Pneumococcal Type	Virulence for mice	Bacteriostatic dose <i>in vitro</i> units per cc	Per cent of Mice Surviving			
			Oxford Units per Day			
			300 & 600	75	30	15
Type I	10 ⁻⁸ cc	0.05	74.1	57.8	23.5	16.7
Type II	10 ⁻⁸ cc	0.025	72.5	15.0	8.3	—
Type III	10 ⁻⁸ cc	0.05	15.4	—	0.0	—

Infecting inoculum 10⁻² cc of culture

Penicillin given in 3 divided doses at 4 hour intervals

The rate of killing by penicillin (bactericidal effect) *in vitro* was the same for each of the three types

of the mice. Explanation of this phenomenon is difficult unless penicillin exerts a direct bactericidal effect in the presence of a systemic infection with pneumococcus Type I. The participation of specific antibodies, in the light of our present knowledge, seems unlikely, although not completely ruled out. These data are shown in Table II.

When either 300 or 600 Oxford units of penicillin are given over an 8 hour period, 74 per cent of the Type I infected animals survive—the maximum effect being achieved at 300 units, with no improvement on increasing to 600 as shown in Table II. At a dosage of 75 units about 58 per cent survive, this decreases to 23.5 per cent at 30 units and is only 16.7 per cent when 15 units are used. It should be noted that 15 units per day in 3 divided doses of 5 units each, given on each of 4 successive days will effect recovery in almost 100 per cent of the animals. However, with this dosage given on a single day, the recovery rate is low.

As previously stated, sulfadiazine administered for a single day is ineffective, even though given at maximum dosage and using the same strain of pneumococcus Type I as in the penicillin experiments. There is apparently a considerable difference in the nature of the antibacterial action of the drugs, sulfadiazine being purely bacteriostatic, whereas penicillin is rapidly bactericidal particularly at high dosage. It has been

estimated that against organisms susceptible to both, penicillin is about 1000 times as active as sulfadiazine. This purely quantitative difference is most important, but it seems proper to emphasize that the qualitative difference may be of even more significance. At lower dosage penicillin behaves more like sulfadiazine, that is, as a bacteriostatic agent, but in a high dosage it is bactericidal.

Pneumococcus Type II behaves somewhat similarly to Type I in mouse infections treated with penicillin, however, it is only at the larger dosages that treatment for a single day has much effect, as shown in Table II. With Type III the effect is considerably less, so that even at dosage of 300 or 600 units per day only 15 per cent of the mice survive. It should be noted that with all three types the virulence was the same in that 10^{-8} cc of culture (1-5 organisms) killed control mice uniformly. The infecting inoculum in each case was 10^{-2} cc of culture corresponding to 1,000,000 lethal doses. *In vitro* the amount of penicillin required to produce bacteriostasis was the same within the limits of error of the dilution method of assay, and each of the strains was killed at the same rate by penicillin *in vitro*. From these studies it is apparent that one cannot carry over to the animal body the results of studies of susceptibility to penicillin *in vitro*, since all three types of pneumococcus behave very similarly *in vitro*, yet *in vivo* differ greatly.

The differences in behavior *in vivo* remain unexplained. It may be suggested that part of the bactericidal effect observed *in vivo* with penicillin is due to the participation of some component of the animal body. This component is most effective against Type I in the presence of penicillin, less so against Type II and even less effective against Type III. Despite these differences in respect to the three pneumococcal types it is apparent that penicillin exerts a direct bactericidal effect when large doses are used in the treatment of mice infected with pneumococci of these three types.

If therapy with penicillin is prolonged for four days, a high proportion of cures can be obtained even in the case of infection with pneumococcus Type III, as shown in Table III. The rate of recovery is proportional to the dosage of penicillin, and for both Type II and Type III much larger amounts are required than for Type I, which it should be recalled, responds best of the three types to treatment given on one day only (Table II). The degree of response to the four day treatment at all dosage levels, but particularly 75 units per day, cor-

TABLE III

EFFECT OF PENICILLIN GIVEN FOR 4 DAYS TO MICE
INFECTED WITH PNEUMOCOCCI

<i>Pneumococcal Type</i>	<i>Virulence for Mice</i>	<i>Bacteriostatic in vitro units per cc</i>	<i>Per cent of Mice Surviving</i>			
			<i>Oxford Units per Day</i>			
			300	75	30	15
Type I	10 ⁻⁸ cc	0.05	—	100.0	97.4	100.0
Type II	10 ⁻⁸ cc	0.025	94.7	60.0	8.3	—
Type III	10 ⁻⁸ cc	0.05	88.5	46.2	3.9	—

Infecting inoculum 10⁻² cc of culture.

Daily dose of penicillin was administered in 3 divided doses

The rate of killing by penicillin (bactericidal effect) *in vitro* was the same for each of the three types

responds roughly to what we know of the antigenicity of these three types. That the development of specific immunity has probably only a minor bearing on recovery, however, is shown by the data in Table IV.

Mice recovering from infection following treatment with penicillin were tested ten days later for specific active immunity by reinfesting them with relatively small doses of homologous strains of pneumococci, as shown in Table IV. The reinfesting dose was very small for all three types, but especially for Type II and Type III. It was found that most of the mice recovering from infection with Type I were immune to reinfection. Approximately one-half of the type II infected mice only had developed immunity even though they had previously recovered from infection with the homologous strain. Of the type III infected mice which had recovered following penicillin treatment, only 12 per cent were immune to reinfection with as little as 100 lethal doses. The percentage of animals immune to the respective types in this penicillin treated series is almost exactly the same as had previously been found for normal mice immunized with a single dose of heat-killed organisms as is shown in Table I. In other words, penicillin did not affect the immune response in demonstrable fashion, and most of the type III infected mice and half of the type II mice recovered without evidence

TABLE IV

ACTIVE IMMUNITY IN PENICILLIN TREATED MICE

<i>Type of Pneumococcus</i>	<i>Reinfecting Dose (M L D)</i>	<i>No. of Mice</i>	<i>Per cent Immune (Survivors)</i>
Type I	1000	38	94.2
Type II	100	62	51.6
Type III	100	33	12.1

Mice had recovered from original infection following treatment with penicillin. Immunity to reinfection with homologous strain was tested 10 days after original infection.

of the development of specific immunity.

From the data presented in Tables II, III and IV it appears probable that an immune response to the infecting agent is not as important a prerequisite for successful therapy with penicillin, as seems to be true for the sulfonamides. With penicillin therapy on a single day only, approximately $\frac{3}{4}$ of type I and II infected mice recover, presumably before specific immunity has had a chance to develop. Similarly, almost 90 per cent of type III infected mice recovered following high dosage of penicillin for 4 days, and on subsequent test only 12 per cent of the recovered mice were immune to type III. An antibody response, therefore, seems of much less importance to successful therapy with penicillin than with the sulfonamides.

The possibility still remains that an effective level of antibodies might develop within 12-16 hours of infection in the case of type I and type II, and that the amount developed in animals recovered from type III infections is too small to detect even by the most sensitive of methods—that is, testing for the presence of active immunity. This is unlikely. The tentative conclusion has been drawn that though specific antibody is probably not the somatic component participating in the bactericidal effect of penicillin in systemic infections, some auxiliary component or components, whose nature is at present unknown, do participate.

It has been assumed in the foregoing discussion that certain more obvious factors have been taken into consideration in the choice of a

therapeutic agent Among the most important of these are that the microorganisms causing the infection must be susceptible to the action of the drug employed, that the drug can diffuse into or be introduced directly into the infected area, and be maintained there in adequate concentration, and that local factors such as inhibitors or unfavorable pH do not nullify its action

Drug fastness or resistance Sulfonamide fastness may be an inherent property of all members of a species or genus of bacteria For example, indifferent streptococci have been found to be highly resistant to this group of drugs even though they have not previously been in contact with a sulfonamide. One may speak of such fastness as natural in contrast to the acquired fastness which may develop in a previously susceptible strain of bacteria during the course of treatment, particularly if the latter be prolonged

Acquired fastness is a commonplace finding during sulfonamide therapy, particularly with staphylococci, gonococci and to a lesser extent, pneumococci Staphylococci possess the ability to become fast fairly rapidly not only to the sulfonamides, but also to gramicidin and penicillin For this reason, in addition to the circumscribed, walled-off lesion which they cause characteristically, staphylococcal infections present a somewhat unique problem in chemotherapy

In the first few years following the introduction of the sulfonamides, the proportion of cures in acute anterior urethritis was variously reported as between 85 and 95 per cent Since then, however, the cure rate has fallen considerably under sulfonamide therapy It is held by some that the decrease in cures is apparent rather than real and reflects principally improvement in the methods used to determine whether cure has occurred On the other hand it has been demonstrated that sulfonamide-fast gonococci are encountered commonly at present, whereas during the early days of sulfonamide therapy this is believed not to have been the case In many clinics, determination of the sulfonamide resistance of gonococci is used routinely as a guide to therapy This would seem to be an important part of diagnosis, since susceptibility of the infecting strain as measured *in vitro* appears frequently to parallel the susceptibility of the human infection to sulfonamide therapy

If a strain of bacteria is fast to one sulfonamide, for example, sulfadiazine, it is fast also to other sulfonamides such as sulfapyridine or sulfathiazole Moreover, fastness once acquired persists in organisms

through an indefinite number of transfers in artificial culture media or animal passages. Acquired fastness to the sulfonamides, however, does not extend to penicillin, which may be used for the treatment of sulfonamide-fast infections.

The evidence obtained up to the present time indicates that penicillin fastness develops less readily than fastness to sulfonamides. In addition to this, penicillin causes the organism to disappear more rapidly, so that its use appears to be distinctly advantageous in infections where fastness to sulfonamides develops frequently, such as in gonorrhea.

The possibility of sulfonamide fastness should be kept in mind in other infections which respond poorly to therapy. It is desirable, if possible, to determine whether the infecting organisms are fast when tested *in vitro*, since it is only by such measurements that one can obtain eventually an appreciation of the problem of fastness and whether or not it is increasing progressively.

Inhibitors of chemotherapeutic drugs. Some sulfonamide-susceptible strains of bacteria produce inhibitor normally during growth, but in amount insufficient to interfere with the bacteriostatic action of the drug. On the acquisition of sulfonamide fastness the amount of inhibitor may be increased greatly with some strains, but fastness of equal degree may be present without any measurable increase in inhibitor production. Sulfonamide inhibitors may also appear in certain lesions, particularly if tissue breakdown is occurring, and in some instances account for failure of sulfonamide therapy. Failure of sulfonamide therapy in localized purulent infections, however, may occur in the absence of inhibitors which are demonstrable by the usual *in vitro* techniques, as mentioned previously in the case of experimental empyema of rabbits.² In some instances no inhibitor could be demonstrated in the pus, yet local therapy with sulfonamides was completely ineffective in sterilizing the lesions. In addition, Tillett³ has shown that empyema fluid from patients does not always contain sulfonamide inhibitor, yet local therapy with these drugs is unsuccessful. As suggested earlier, the failure of local sulfonamide therapy may be based commonly on factors other than inhibitors, and the success of penicillin under these circumstances due not so much to the absence of penicillin inhibitors as to the bactericidal properties of this compound.

In passing it may be mentioned that certain organisms both gram positive and negative, may elaborate an enzyme, penicillinase which

destroys penicillin. The importance of this enzyme as a cause of failure of penicillin therapy has not been adequately assessed.

Nature and location of the lesion. Lesions produced by staphylococci characteristically localize early and become surrounded by a pyogenic membrane which prevents diffusion of chemotherapeutic agents into them. If therapy has not been begun before walling-off has taken place, it may be necessary to eradicate the local lesions by surgical procedures or else introduce adequate concentrations of penicillin directly. The sulfonamides exert little effect on localized staphylococcal infections, though they may be lifesaving in preventing overwhelming systemic infection. Their failure locally may be attributable to the presence of sulfonamide inhibitors, acid reaction of the pus or absence of specific antibodies and functional phagocytes which appear to be essential for the therapeutic action of these bacteriostatic compounds. It seems probable that the failure of the sulfonamides in the treatment of tuberculous infections may be attributable to the same factors, since it has been shown *in vitro* that the tubercle bacillus is susceptible to their bacteriostatic effect.

Factors other than a pyogenic membrane may prevent diffusion of a chemotherapeutic agent into the involved area. Most of the sulfonamide drugs pass readily into the cerebrospinal fluid and hence treatment of meningitis with sulfonamides can be carried out without recourse to intrathecal administration. This is a distinct advantage in the therapy of meningococcal meningitis. Penicillin is extremely active against the meningococcus but following intramuscular or intravenous injection very little of the compound appears in the cerebrospinal fluid. It must therefore be injected intrathecally, as well as by other routes in treating meningitis.

Difference in the rate of antibacterial action of the sulfonamides and penicillin. An additional factor which should be taken into consideration in choosing a chemotherapeutic agent is the difference in the rate of antibacterial action of the sulfonamides and penicillin. It has been demonstrated both *in vitro* and in the animal body that a lag phase occurs in the action of the sulfonamides. For a period up to four hours or even longer, susceptible bacteria exposed to an effective concentration of a sulfonamide, multiply at a normal rate. Following this initial lag phase, multiplication ceases. Under many circumstances this delay in bacteriostasis may not be important. On the other hand, in a rapidly

progressing infection such as fulminating meningococcal meningitis, or in an infection not treated until considerably advanced, the lag phase in sulfonamide action might conceivably be sufficient to permit a fatal outcome. Similarly, in infections caused by bacteria which produce potent exotoxins such as the gas gangrene anaerobes, the amount of toxin produced by the organisms in a massive area of infection during the sulfonamide lag phase, might also be seriously detrimental. This lag phase, so characteristic of the antibacterial action of the sulfonamides, is not encountered with penicillin *in vitro*, and so far as present data go, does not occur to a significant degree in the animal body. Under the conditions enumerated immediately above, penicillin would appear, therefore, to be a more appropriate therapeutic agent. This view would appear to be even more valid, if one adds to the lack of a lag phase the primary bactericidal properties of this drug as discussed earlier, which require less active participation of the body defense mechanisms than in the case of the sulfonamides.

SUMMARY

1. The sulfonamide drugs are strictly bacteriostatic and require for their most effective action the participation of specific antibody and an active phagocytic system in curing infections due to susceptible organisms.

2. Penicillin exerts a direct bactericidal effect in the animal body as well as in the test tube, and hence its therapeutic efficacy is not as dependent on the development of specific immunity as in the case of the sulfonamides. This does not imply that specific immunity may not be very desirable as an adjunct to penicillin therapy under certain circumstances.

3. Equal and marked susceptibility of bacteria to the effect of penicillin in the test tube, even of members of the same species, as in the case of pneumococcus Types I, II and III, does not mean that infections caused by them will respond equally well. It should be noted that the same is true of sulfonamide therapy, since bacteria of the same susceptibility *in vitro*, for example the above strains of pneumococcus, Types I, II and III, differ greatly in their response to the sulfonamides in the animal body.

4. Failure of sulfonamide therapy in localized purulent infections, even though introduced directly into them, is due in all likelihood to a

number of factors the presence of sulfonamide inhibitors, an unfavorable pH, development of sulfonamide fastness, and the absence from the lesions of specific antibody and functional phagocytes

5 Under certain circumstances the immediate antibacterial effect of penicillin, as contrasted with the lag phase characteristic of the action of the sulfonamides, may be of importance in determining which therapeutic agent should be used

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BULLETIN OF
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AUGUST 1945

AIR-BORNE INFECTION
THE RATIONALE AND MEANS OF
DISINFECTION OF AIR*

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“THE prevention and control of acute disease of the respiratory tract is the most serious problem and at the same time the most urgent challenge that today confronts medicine in general and industrial medicine in particular. Although diseases and injuries of occupational origin have long claimed the chief interest and attention of physicians in industry, it is now well established and generally recognized that in their frequency and importance non-occupational diseases far outweigh those conditions which arise from industry. The latter are chiefly responsible for stupendous losses in both time and money to employer and employee alike.”

The sentences quoted opened an address by George Morris Piersol¹ at the Third Annual Congress on Industrial Health in January, 1941.

The acute respiratory infections are of course a challenge in family

* Earlier articles by the present author: Current Progress in Sterilization of Air, *Am Jour Public Health* 34:578-586 (June) 1944 and *Brit Med J* 2:67-70 (July 15) 1944, and Confined Air as a Vehicle of Infection, Current Progress in Air Sanitation, *Med. Clinics of North America* W. B. Saunders Co., Phila., Nov., 1944, have been extensively drawn upon in the preparation of this lecture.
This paper presented November 2, 1944 at the Stated Meeting of The New York Academy of Medicine in the first A. Walter Sutter Lecture.

and military practice quite as much as in industrial medicine. Because quantitative data are available for industry, however, it will be convenient to examine the consequences of respiratory disease with particular reference to industrial disability. Does examination of available data on industrial disability due to acute respiratory disease indicate that this challenge is being met in current practice? Quite the contrary. The frequency of sickness and non-industrial injuries causing disability for 8 consecutive calendar days or longer among a very large sample of industrial workers over the years 1933-1943 has been analyzed by the U. S. Public Health Service^{2,3}. Sickness absenteeism among males due to respiratory disease has shown a steadily mounting rate since 1938, the rate for 1942 was higher than in any previous year of the ten-year period, 1933-42. For females the rate was steady from 1939 through 1942 but at a high level. In 1943³ there was further striking increase in frequency of the respiratory group of diseases, the male and female rates being 61 and 57 per cent in excess of the corresponding rates for 1942, and 78 and 58 per cent in excess of their 10 year means, covering 1934-43. In the first two quarters of 1944 respiratory disease rates were just below their values for the corresponding quarters of 1943. Influenza and grippe, bronchitis, acute and chronic, pneumonia, all forms and "other respiratory diseases," including colds, sinusitis, laryngitis, pleurisy, asthma, and "respiratory infection" are chiefly responsible for the excessively high total rate.

This high and mounting rate of industrial disability from respiratory disease has been maintained during the years of the present war in opposition to the long range trend in respiratory disease mortality rates, this trend, with the notable exception of the years of the first World War and influenza pandemic, has been downward since 1900.

Whatever are the causes of this increasing rate of industrial disability due to respiratory disease, common sense cautions us not to seek the complete explanation in the conditions of work in industrial establishments alone. The packing of industrial and other workers in the ill-ventilated common carriers, trains, street cars, and busses, since rubber and gasoline shortages have been over-taxing already taxed transportation facilities, certainly provides one superlative opportunity for the spread of endemic and epidemic respiratory disease, crowded and confined places of amusement provide another.

In attempting to form even a rough estimate of the cost of this

industrial disability, recourse may be had to smaller samples which have been subjected to more detailed analysis. Figures for a public utility for the period 1938-1942, inclusive, have been published,^{4 5} these show that days lost from respiratory disease are more than a third of the total days lost from all causes of disability. The absences lasting one calendar day or longer in a sample comprising about 2,500 male and 550 female employees in a public utility in 1942, yielded an average loss due to respiratory disease for males of 3.1 days, for females of 4.3 days. It is of course understood that the figures for one company cannot be taken as representative of conditions in American industries as a whole. These rates may be either too high or too low. To gain an idea of the approximate cost, if these rates were representative, however, we may multiply these rates by the numbers of non-agricultural workers in the United States, these were approximately 26 million male and 14 million female workers. This yields an approximate total (with the reservations mentioned) of over 80 million man-days and over 60 million woman-days (or over 140 million person-days) lost to industry in the United States through respiratory disease in 1942. On the basis of 300 working days per year, this waste is approximately equivalent to the time of 470,000 persons working for a year.

The Bureau of Labor Statistics publishes monthly data on straight-time hourly earnings for manufacturing industries in the United States as a whole.⁶ The author has computed an average daily earning by multiplying the straight-time hourly earnings (80.5 cents) by 8, the normal working day in American industry.* On this basis the loss in wages due to respiratory sickness amounted to roughly \$900,000,000 per annum. This does not include the expenses for medical care, overhead expenses arising out of idle machinery and interruption in production schedules, and other items.

The figures above are for 1942, it has already been indicated that respiratory disease rates in American industry in 1943 were even in excess of those in 1942.⁸ The average number of days lost from respiratory diseases in the above public utility during 1943 was for males 4.5 days and for females six days.⁷ The estimates for June 1943 of the number of employed non-agricultural workers in the United States⁸

* It is unfortunate that daily rates of pay are not available. Since the figure representing costs of time lost due to respiratory disease is at best only an approximate one the straight hourly earnings (excluding overtime earnings) are multiplied by 8 to secure a daily wage. It is recognized that this is somewhat arbitrary.

were males, 28.6 million, and females, 15.6 million. Calculated on the same basis as above these data yield an approximate total of 128 million man-days and 93 million woman-days or over 220 million person-days lost to industry in the United States through respiratory disease in 1943, equivalent to a waste of the labor of about 740,000 persons working for a year. The cost calculated as above would be almost 1.5 billion dollars.

Although the desirability of ameliorating disease responsible for so great a wastage in time, money and well-being would seem to be self-evident, this desirability has been questioned, notably in the interesting volume on "Air-Borne Infection" by Dwight O'Hara,⁹ from which we quote

"From a sufficiently detached and objective point of view it is possible to look upon the present prevalence of respiratory infection with some satisfaction and equanimity, for it is more responsible than any other factor for keeping the population ready and resistant to that greatest cold—pandemic influenza—which might otherwise be a much more frequent and deadly visitor. The writer prefers to think of them (the costs) as a reasonable price paid for the preservation of some semblance of respiratory resistance, for an initial resistance to invasion may be cheaper to maintain than to dispense with, biologically as well as socially and politically. Let us not be too impatient with our yearly colds; they keep us from becoming immunologically soft, as we assuredly do when we successfully isolate ourselves from them for any long period."

However, influenza virus of Types A and B are currently each being used successfully for active immunization against epidemic human influenza of corresponding type. Cross protection is not demonstrable between types A and B. The causal agent of pandemic influenza is unknown. The justification for assuming that the miscellaneous and miserable respiratory episodes of the winter months afford protection against pandemic influenza is therefore not apparent to the present writer. Certainly we would not do well to rely upon such haphazard means. It seems to the writer more likely, indeed, that the emergence of pandemic influenza is preceded by the appearance somewhere in the world of a mutant virus of peculiarly high communicability. In this case the prevailing conditions permitting universal dissemination of respiratory flora are less a safeguard than an invitation to disaster.

Against what, then, might we become "immunologically soft", lacking the banal respiratory infections? There is evidence that the virus or viruses of the common cold do afford some transient increase in resistance, but this does not last for most persons even through a single winter, and can hardly be regarded as of long range value. Is it against the common bacterial secondary invaders, pneumococci, hemolytic streptococci, influenza bacilli or staphylococcus? Protection against invasion by each of these bacterial species is known to be specific for type, and fifty odd types of pneumococci,¹⁰ forty odd types of *Streptococcus pyogenes*¹¹ and at least six types of *Hemophilus influenzae*¹² are now recognized. It is possible that a useful degree of resistance against the prevailing flora might be built up temporarily within an isolated population, such as that on a ship at sea, but in ordinary life, with innumerable opportunities for interchange of respiratory flora at work, on the way to and from work, and in homes and places of recreation, there seems to be little bacteriological or immunological basis for expecting benefit from infection. Moreover the respiratory pathogens are not well adapted to propagation or even long persistence on normal mucous membranes. Reduction of the means of dissemination of pathogens would unquestionably result in a reduction of morbidity, and a corresponding reduction in carrier rate and in the prevailing prevalence of infectious agents.

Nor do relevant epidemiologic facts sustain the argument against suppression of the vehicles of respiratory infection. Rates of respiratory disease, as is well known, tend to show a lesser early winter and a greater late winter peak. The early winter peak doubtless reflects renewed exposure of a population with a diminished resistance against certain pathogens, but the peak in the late winter or early spring is characteristically higher both with respect to morbidity and to severity of complications, and this unquestionably reflects the widespread dissemination during the winter of viral and bacterial pathogens. Finally there is the actual record showing a steady building up of rates of respiratory infection from 1938 through 1943, contrary to the long range trend. If an effective resistance were purchasable at the price of frequent infection, this should automatically check the rise in infection rates. Infection rates on the contrary have continued upward even at an accelerating pace under conditions in the war years.³

Carrying the thought further, it seems unlikely, too, that abolition

of water sanitation or pasteurization of milk would be advocated on the grounds that these measures make us "immunologically soft" with respect to intestinal infection (although T E Lawrence in his *Seven Pillars of Wisdom* does smile at the expense of newcomers to Arabia because they cannot drink with impunity from desert water holes) Vaccination can keep the immunologic mechanism in function, if necessary, more surely and more systematically than can haphazard natural infection

'Sufficient unto the day is the evil thereof' The evils of respiratory infection are unequivocal, in the author's belief the means of dissemination of respiratory disease agents should be attacked whole-heartedly, uninhibited by concern over remote possibilities should we succeed beyond our hopes In fact what is done in the next decades to understand and control air-borne infection may be taken as a significant index of how well we have learned one lesson of the war, that the broadest possible development of pure and applied science is fundamentally related to national security and well-being

RELATIONSHIP BETWEEN RESPIRATORY DISEASE AND THE INFECTIOUSNESS OF AIR

Persons sneezing, coughing, or even speaking loudly expel into the air large numbers of minute droplets which may contain in a viable and infective state any pathogenic bacteria or viruses present in their oral secretions The larger of these potentially infectious droplets have a flight range of about a meter, they are conspicuous, are easily recoverable on bacteriological plates, and their ability to transmit respiratory infection is obvious When droplets or sputa have dried on solid surfaces their residues may become the source of infective dust

The role of droplets was notably stressed by the German hygienist Flügge in 1897,¹³ and the doctrines of "droplet-infection" and dust-infection, or transmission of respiratory infection by droplets and by infective dust dominated thinking in regard to respiratory disease for thirty years *

The greater part of the potentially infective material expelled by persons into the air, however, is not contained in droplets visible without special means, but in smaller droplets which evaporate almost in-

* Actually, however, Flügge himself appreciated the importance of invisible droplets accompanying the coarser visible droplets, these he recognized may persist in air for hours and reach distant parts of enclosed spaces

stantaneously The basic experimental demonstration was made by Wells^{14, 15} in 1933-1934 that much of the enormous germ-load conveyed to the atmosphere by the evaporated residues ("droplet-nuclei") of these finer droplets, remains viable for hours or even days in the air of enclosed spaces and is wafted about like smoke to convey pathogenic bacteria or viruses to those who share the confined air

The atomizing of mouth and nose secretions into the air has lately been revealed with dramatic vividness by high-speed photography^{16, 17} Many such photographs analyzed by Jennison showed in each sneeze about 20,000 droplets, ranging in size from about 10 μ to about 400 μ , between 40 and 80 per cent of these droplets were estimated to have diameters less than 100 μ and hence to be of the size which evaporated in the air to form potentially infective "droplet-nuclei" Photographs of sneezes through surgical masks of increasingly fine mesh show increasing efficiency in screening out droplets Other pictures suggest that conscious effort in stifling a sneeze with handkerchief or even with the hand can materially reduce the germ-load conveyed to the air and the resultant public health hazard Contamination of the air is not limited to sneezes, as is illustrated by photographs which show the droplets resulting, respectively, from a cough and from enunciating loudly the consonant *F* Jennison's analysis shows that coughing or loudly speaking the consonants *F*, *P*, *T* and *S* may produce from a few dozen to a few hundred droplets The subject has been comprehensively reviewed by Jennison^{16 17}

The enormously important role of pathogens floating in confined air in the dissemination of respiratory disease has now been adequately documented by animal experiments, by observations in controlled human environments, and by epidemiological deductions, the evidence to 1941 has been conveniently assembled in the volume *Aerobiology*, published by the American Association for the Advancement of Science with the aid of the Committee on Aerobiology of the National Research Council

Any attempt to appraise current progress in the sterilization of air must, however, take account of the historical background Members of the medical profession who now occupy responsible positions in practice, in teaching and in administration have been thoroughly trained in the doctrine of "droplet-infection" Recognition of the greater importance of true air-borne infection has only come within the past ten

years, and has deeply impressed only the relatively small number of those who have seriously examined evidence which is either very modern or very old, (of course important foundations of the germ theory of disease were laid by the studies of Pasteur, Tyndall, and others on microorganisms in the air) Lack of a more insistent demand on the part of the medical profession for practical solution of the problems of air-borne infection might seem incomprehensible if this background were lost sight of Lacking adequate demand by many prominent members of the medical profession for progress in securing pure air supplies, hygienic practices, as well as social customs, from the standpoint of health at least, have somewhat neglected the main point The point is that, just as intestinal disease has in considerable measure been controlled by reducing the germ-load of water and milk, for the control of air-borne respiratory disease practical measures for reducing the germ-load of confined air must be instituted

The technical devices used for quantitative estimation of the germ-load of air are currently subjected to critical comparison by du Buy and Hollaender^{18, 19} Determination of the number of microorganisms in a given air volume is performed by samplers which follow one of two principles impingement on solid media or atomization in liquid media The group of atomizing devices gave bacterial counts from 10 to 30 times higher than the impinging devices Analysis of this difference showed that it was mainly due to the fact that air-borne microorganisms may occur in clusters, each cluster is counted as one colony in the impinging devices but the clumps are more or less broken up in the atomizing devices The authors recommend that

"Information on the manner in which microorganisms occur in a certain airspace should therefore cover the following points

- 1 The total number of organisms present, singly or in clusters An approximation to this number is given by the atomizing devices

- 2 The number of particles or droplet nuclei, which contain microorganisms, either singly or in clusters, and which remain suspended in the air or are in the process of settling This number is approximated by the impinging devices

- 3 The number of particles or droplet nuclei, containing microorganisms, which are heavy enough to settle through gravity The open plate method supplies this information"

CONTINUOUS DISINFECTION OF AIR

Effective continuous disinfection of the air of enclosed spaces has already been shown to be practicable where conditions are favorable and where the problem is approached with adequate determination and technical facilities and skill. The practical means are physical (ultra-violet radiation,^{15, 20} dust-suppressive measures^{21, 22}), and chemical (germicidal vapors^{23, 24, 25}). Doubtless physical and chemical means will each find appropriate place as mutually complementary measures in the fully matured art of providing non-infectious air in our future homes, transport vehicles, and places of work and recreation. *Ultra-violet Radiation*. Application of ultra-violet radiation to disinfection of air has been systematically reviewed in the A A A S volume on *Aerobiology*. The physiological and the germicidal effects of ultra-violet radiation, and the characteristics and standardization of commercially available ultra-violet sources are presented in detail. Successful application of ultra-violet irradiation to reduction of wound infections in the operating room are presented by Deryl Hart, the pioneer in this field, and by Kraissl and Wilson of Columbia. Cross-infections in hospital wards and in children's nurseries and schools are reviewed and analyzed, and success in reduction of these cross-infections by appropriate use of ultra-violet irradiation is recorded. More detailed analyses of successful control of childhood contagions in schools have been published by Wells, Wells and Wilder,²⁶ and by Wells and Wells.²⁷

More recent records of germicidal action against bacteria and viruses by ultra-violet radiation in a children's hospital, with reduction in cross-infection, have been published by Robertson, Doyle, and Tisdall,²⁸ by Sommer and Stokes,²⁹ and Henle, Sommer, and Stokes.³⁰ The Council on Physical Therapy of the American Medical Association has found ultra-violet lamps acceptable as an adjuvant in the disinfection of air,³¹ and commercially available burners and fixtures of several types have been approved by the Council³² for use in the operating room, hospital nursery, and hospital ward.

The statement of the Council on Physical Therapy on acceptance of ultra-violet lamps for disinfecting purposes contains carefully considered appraisal of the present status of the practical art. Pertinent statements are quoted below.³¹

"At the present juncture the design and installation of ultra-violet

lamps in their fixtures for disinfecting purposes is empirical and the adequacy of disinfection by any given installation of lamps must be judged by clinical experience. For example, clinical evidence has been submitted to the Council showing that, in a scarlet fever ward (size about 60 by 27 by 11 feet) containing sixteen cubicles, four lamp units, each one emitting a radiant flux of 30 microwatts per square centimeter at 1 meter, were found inadequate, but eight lamp units in the ward, each unit protecting two cubicles, and a ninth unit at the entrance, prevented cross-infection. This is a rather high intensity (requiring twenty minutes calculated time to produce a minimum perceptible erythema) incident on a person of average height, standing directly under a lamp fixture suspended from a ceiling of average height. A greater number of lamps, each one of lower ultra-violet intensity (say 20 microwatts per square centimeter at 1 meter) and lower power input, more evenly distributed throughout the room should be safer and equally efficient in disinfecting the air. This is a matter of engineering design, beyond the scope of the Council's purview.

"Since the ultra-violet emission from the low vapor pressure mercury discharge tube is practically homogeneous radiation of wavelength 2,537 Å, such a lamp can be readily calibrated in absolute value and used as a standard. The intensity at 1 meter may be only one-fifth of the Council's unit, or 20 microwatts per square centimeter, for safety to the occupants. This will require a minimum exposure of two hundred and fifty to five hundred seconds for adequate disinfection, which will depend on the rate of circulation and average distance of the air in front of the lamp. Evidence has been submitted to the Council showing that cross-infection in a contagious ward may be prevented by using a sufficient number of lamp units, each unit having an intensity of 30 microwatts per square centimeter at a distance of 1 meter from the burner. This will require an exposure of one hundred and sixty-seven to three hundred and thirty-four seconds for adequate disinfection, which implies a slow movement of the air in front of the lamp installation.

"The use of ultra-violet radiation for disinfecting air in industrial plants, barracks, school rooms, assembly halls, refrigerators and so on also appears to be outside the Council's purview. In fact, at this juncture the whole question of the use of ultra-violet radiation for disinfecting purposes is too complex and too little understood for the

Council to do more than attempt to keep the medical profession informed regarding particular ultra-violet lamps that are acceptable for use in this method of disinfecting air in hospitals, nurseries and operating rooms (relatively free from dust) as practiced by present day empirical methods "

It must be emphasized that the Council's acceptance statement does not prejudge the applicability and the usefulness of ultra-violet radiation to the problem of disinfecting the air of industrial plants, offices, assembly halls, railroad cars, etc. It emphasizes, however, that the specifications of engineering design and other features determining the adequacy and safety of the practical art must be further developed and applied before evaluation will become possible

Another paragraph of the Council's statement discusses responsibility for design of installations

"It is to be noted that a lamp used for disinfecting purposes is a single unit in an installation, and that compliance of the ultra-violet output of a single lamp unit with the Council's requirements does not insure adequate radiant disinfection or the safety of the occupants of the room in which an installation of such lamps is in actual use. Obviously the manufacturer and distributor of such lamps must assume some responsibility for the adequacy of the lamp installation for purposes of radiant disinfection of the air and for the adequacy of the protection from injury of the occupants of the space irradiated. Concerning these questions the Council cannot undertake supervision or assume responsibility for the satisfactory performance of any particular installation "

The Senior Biophysicist of the Division of Industrial Hygiene, National Institute of Health, (who also is Referee for the *APPEAL* on Disinfection of Air by Ultra-Violet Irradiation), has critically reviewed applications, precautions and limitations of the use of ultra-violet irradiation to disinfection of air. The statement of the Council on Physical Therapy is quoted with approval. The manufacturer and distributor of such lamps must assume responsibility for the adequacy of the lamp installation for purposes of radiant disinfection of the air, and for the adequacy of the protection from injury of the occupants of the

Acceptance by the architectural
province air hygiene may be

of responsibility for elaborating specifications for proper design and servicing of installations would be an important step toward development of a practical art of air hygiene. In this connection it is encouraging to note the recent formation of a Technical Advisory Committee on Air Sterilization and Odor Control of the American Society of Heating and Ventilating Engineers³⁵

The efficacy of ultra-violet irradiation in killing air-borne bacteria and viruses under conditions in which the air is relatively free from dust and lint has been confirmed in Great Britain by Andrewes and others³⁰ and by Edward, Lush, and Bourdillon³⁷. The difficulty of disinfecting dust-laden air by this means has also been emphasized. Andrewes *et al*³⁶ suggest the combination of air filtration and ultra-violet irradiation in recirculation systems and for certain special purposes.

Complete success in controlling the spread of a specific air-borne disease under rigid experimental conditions has recently been recorded by Lurie³⁸. A rabbit colony, 73 per cent of whose unprotected control animals developed progressive tuberculosis, was completely protected from tuberculosis by ultra-violet irradiation over the period of the experiment (almost a year). The author concludes:

"The contagion of tuberculosis in these studies is air-borne and the radiant energy exercises its protective influence by its bactericidal properties. It is probable that ultraviolet irradiation may control air-borne contagion of human tuberculosis."

A factor of critical importance in determining practical success or failure is illustrated by recent experiences relating to control of colds. The Cradle Society in Evanston, Illinois, erected in 1939 a new building specifically planned in reference to controlling respiratory infection³⁹. Infants are cared for from shortly after birth until adoption. The normal infants receive care under strictest nursing precautions in wards of three types: (1) units provided with modern air-conditioning but (from 1939 to 1942) without additional protection, (2) similar air-conditioned units protected from air-borne infection by ultra-violet irradiation of the barrier type designed by W. F. Wells, (3) air-conditioned units protected by special mechanical means designed by J. A. Reyniers.

Primary introductions of colds into the institution occurred through nurses contracting colds and by admission of new infants with colds. Infections contracted from these infected sources were for three years

TABLE I
INCIDENCE OF RESPIRATORY INFECTIONS AT THE CRADY

	<i>Period from April 1, 1939 to March 31, 1942</i>			<i>Period from April 1, 1942 to September 30, 1944</i>	
	<i>Number of Primary Infections</i>	<i>Number of Secondary Infections</i>		<i>Number of Primary Infections</i>	<i>Number of Secondary Infections</i>
Control Unit without germi- cidal lamps	43	21	Control Unit with germi- cidal lamps	39	2
Wells Unit	45	1	Wells Unit	40	1
Reyniers Unit	49	1	Reyniers Unit	46	3

This table is published here through the courtesy of Iwan Rosenstern⁴⁰

practically limited to the air-conditioned control units, as shown in Table I⁴⁰ At this time it seemed no longer justifiable to continue the air-conditioned units without further protection and ultra-violet burners of the wall-bracket type for upper-air irradiation were installed in the control wards Since then secondary respiratory infections have been negligibly few in all units Bacteriological studies by Iwan Rosenstern^{39, 40} of the air of the several units under various experimental conditions have been entirely in harmony with the clinical results

In contrast to these successful results in controlling the spread of colds among fully institutionalized infants is the experience with colds in primary schools recorded by Wells, Wells and Wilder²⁶ These investigators were successful with ultra-violet irradiation in controlling childhood infections whose source of contagion is in school, but unsuccessful in controlling colds, presumably because there was adequate opportunity to contract the colds in unprotected environments outside the school, as shown by a uniform daily incidence of colds throughout the week

The critical importance of proper design and adequate intensity of irradiation has been illustrated in a current study of the control of air-borne infection in a naval training station at Sampson, New York⁴¹ Two sets of barracks were equipped with burners arranged to irradiate the air of the barracks above eye level and the floors with ultra-violet radiation One set of barracks received radiation of relatively high in-

tensity, the other of relatively low intensity. Average intensities in both cases, however, were not higher than the levels set by the Council on Physical Therapy, the high intensity exceeded the low intensity level by less than two-fold. Similar barracks were maintained as unirradiated controls in each case. Exceedingly careful epidemiological analysis showed that the ultra-violet irradiation of high intensity was accompanied by a statistically significant reduction of 25 per cent of respiratory illness, whereas respiratory illness in the low intensity barracks did not differ significantly from that in the unirradiated controls.

In view of the critical importance of proper design of ultra-violet installations in governing adequacy and safety, it is fortunate that significant progress is being made in the formulation of specifications. Notable advances in this respect have recently been reported by Wells²⁷ and by Buttolph⁴². Although these matters are in the field of engineering and outside the scope of this lecture, their importance in determining the success or failure of the practical art of air sanitation can hardly be overemphasized.

Germicidal Vapors The spraying of germicides into the air was of course a part of the technique of antiseptic surgery. Modern interest in germicidal mists was stimulated by the demonstration by Douglas, Hill, and Smith,⁴³ Trillat,⁴⁴ and Masterman⁴⁵ that certain bactericidal substances, e.g. NaOCl and a number of phenolic compounds, when dispersed in the air as fine mists or aerosols exerted a highly lethal effect on air-borne bacteria. Twort, Baker, Finn, and Powell^{46, 47} found that hexyl-resorcinol dissolved in propylene glycol made a highly effective and satisfactory aerosol.

An inclusive and practical discussion of the problems of air-borne infection and means for its amelioration in war-time Britain has been presented by Andrewes and others³⁰. Concerning germicidal mists and vapors they conclude

"*Hexyl-resorcinol* in propylene glycol has proved perhaps the most effective under laboratory conditions, but unfortunately neither the antiseptic nor its solvent is at present readily enough available* in large amounts to warrant its introduction except for special purposes."

Considerations of economy and practicability as well as of efficacy have served to focus attention in Britain on the germicidal value of

* Hexyl resorcinol is at present available in limited amounts and the glycols are available in large amounts in the United States.

hypochlorites and hypochlorous acid. Actually the use of hypochlorites for purification of air was first tried in England as early as the influenza pandemic in 1918. Masterman⁴⁸ reviews in detail the early history and various controversial aspects of the use of hypochlorites for air purification. He describes an atomizing device (Dynalysor) as already in successful operation. "For many months the Dynalysor has been successfully employed for hypochlorite spraying in hospitals, offices, and other inhabited rooms, and air purification by hypochlorites is not a scheme 'with definite possibilities' but a successful *fait accompli*." Masterman concludes that HOCl gas is the active germicide in hypochlorite spraying.

Bourdillon, Lidwell, and Lovelock⁴⁹ have reported success with hypochlorite atomized by a hand spray in disinfecting air contaminated by sneezing. They note certain unfavorable conditions, "such as low relative humidity or high content of organic matter in the air, which may hinder the action of hypochlorite sprays." They also note promising results from vaporized lactic acid.⁵⁰

Edward and Lidwell⁵¹ report favorable tests on sterilization of air-borne influenza virus with hypochlorous acid gas.

"A concentration of 1 vol. of gas in 2 million vol. of air is probably effective in destroying 99 per cent or more of virus particles when the proportion of these in the air is small. Preliminary experiments on mice and cats are recorded which failed to reveal any toxic effects produced by inhaling the gas in relatively high concentrations or for prolonged periods. Acute irritation of mucous membranes only was found. This did not appear to lead to any increased susceptibility of mice to subsequent infection with influenza."

Exploration of the possibilities of continuous disinfection of air by chemical substances has made and is making rapid progress in America through the work of O. H. Robertson and his associates. They determined that certain of the glycols alone, notably propylene glycol²³ and triethylene glycol,²⁴ provided promising means for continuous disinfection of air. They demonstrated that the germicidal action depended, not, as earlier supposed, upon collision of fluid droplets with air-borne bacteria, but upon condensation of hygroscopic glycol molecules upon air-borne droplets containing bacteria. One gram of propylene glycol dispersed as vapor in 5 or 10 million ml. of air and 1 gram of triethylene glycol vapor in several hundred million ml. of air was found to kill

pathogenic respiratory bacteria and the virus of influenza in air in seconds or minutes. Rat and monkey colonies kept constantly in atmospheres saturated with vapors of propylene glycol for periods up to eighteen months, and triethylene glycol up to a year suffered no ill effects detectable by observation or microscopic examination⁵⁵ and the animals bore young⁵².

"The germicidal activity of glycol vapors is markedly influenced by certain environmental factors, the most important of which is atmospheric humidity. A dry atmosphere is unfavorable. Likewise desiccated bacterial particles are not as susceptible to the vapor action as are moist ones. It has been found that the glycols are most effective at relative humidities between 40 and 60 per cent."

Subsequent work by Bigg, Jennings, and Fried^{53, 54} places the relative humidity for maximal germicidal action of glycol vapors at from 30 to 50 per cent. These and subsequent papers^{52, 55, 57} indicate the types of apparatus that are being developed for disinfection of the air of large enclosed places by glycol vapors.

Careful investigation of the possibility of fire hazard resulting from the dispersal of glycol vapors into the atmosphere of enclosed spaces has also been made by Bigg, Jennings, and Fried.⁵⁴ These authors conclude:

"In the vapor-phase concentration required for air sterilization, propylene and triethylene glycol offer absolutely no fire or explosive hazard. The addition of water to these substances greatly reduces the possible fire hazard produced by their presence in storage or vaporizing devices."

Most recently, practical apparatus^{56, 57} has been constructed and utilized for introduction into the air of properly humidified glycol vapors. Boiling glycol-water solutions are maintained automatically at any desired relative concentration. The vapors emitted from such boiling solutions are of constant composition and are bactericidal. A predetermined rate of delivery and concentration of water and glycol vapor may be accurately produced by varying, respectively, the heat input and the temperature of the boiling mixture. Apparatus of this type has been given laboratory trial and also practical test in large dormitories. The authors⁵⁷ conclusions are quoted in detail.

"Bactericidal quantities of glycol vapors can be maintained in large occupied spaces for long periods of time. It has been shown that glycol

vapors can be uniformly distributed in large rooms. A means for generating glycol vapors in controlled amounts is described. The occupants of treated rooms experience no discomfort due to glycol vapors. Triethylene glycol is preferred over propylene glycol because much smaller amounts of the former are bactericidal. Optimum bactericidal concentrations required with triethylene glycol range from 0.003 to 0.005 mg per liter of air. Relative humidities in the range 25 to 60 per cent are required for optimum bactericidal action.

"Records were kept of the number of men from each dormitory contracting diseases believed to be air-borne. Studies of the hospital records indicated a noticeable reduction of infections in the test dormitories. The results were very encouraging and further carefully controlled observations with larger groups are being planned."

Clinical application of glycol vapors during the winters of 1941-1942, 1942-1943 and 1943-1944 are recorded by Harris and Stokes^{58 59 60} working at the Children's Seashore House in Atlantic City. This convalescent home has a relatively stable population and the children in the wards are confined to their beds and thus subject to a minimum of contact or direct-droplet infection. Experimental and control wards were carefully matched, control and glycol-vapor wards were alternated for three week periods throughout the respiratory season. Ill effects were not encountered. The germ-load of the air was shown to be greatly reduced by the glycol vapors as judged by direct plate counts. In the preliminary study two respiratory infections occurred in the vapor-containing ward as compared with sixteen in the analogous control ward. During the second winter five respiratory infections occurred in the vapor-containing wards as compared with 100 in the similar control wards without glycol vapor. During the season of 1943-1944 respiratory infections were in the ratio of 6 in the vapor containing to 16 in the control wards.⁶⁰

"The concentration of propylene glycol vapor in air was maintained in the neighborhood of one part in 15,000,000 (0.069 mg/liter). Concentrations at various times and in different parts of the experimental wards ranged from 0.048 mg/liter to 0.094 mg/liter.

"In the case of tri-ethylene glycol the maintenance of a satisfactory concentration presented a greater problem, because of the narrow range between bactericidal concentration and precipitating concentration mentioned above. In the absence of sensitive methods for regulating or

measuring concentrations of tri-ethylene glycol vapor in air, a rate of vaporization sufficient to disinfect the air to a considerable degree was often found to produce precipitation of glycol on windows, floors and objects in the ward. The concentration of this vapor in air ranged between 0.0018 mg/liter and 0.0033 mg/liter.

"The difficulties encountered in this study in the use of tri-ethylene glycol are due largely to the early stage of engineering development of the field, and to the relatively small size of the enclosed spaces involved. In a larger volume of air the fluctuations in glycol concentration caused by occasional opening of doors, etc., would be proportionately smaller and the concentration could be maintained in a narrower range. The ultimate development of devices to regulate the rate of vaporization of tri-ethylene glycol by the concentration of the vapor present in air at the moment may obviate the difficulties in using this disinfectant and permit workers to take advantage of its higher potency.

"At the present writing, however, it would appear that in the absence of refined devices to regulate the rate of vaporization of glycol, propylene glycol is the agent of choice in small wards, offices and spaces of similar size."

In his report as Associate Referee on Disinfection of Air by Germicidal Vapors and Mists, Professor O. H. Robertson writes⁶¹

"Practical application of the use of glycol vapors for the purpose of controlling air-borne infection has had to await the construction of suitable apparatus for the dispersion of glycol vapors into large enclosed spaces and the development of an instrument to control automatically the concentration of glycol vapor in the air. Rapid progress is being made in the solution of both these problems."

Types of vaporizing device for large spaces,^{72 76 57} for smaller spaces^{52 57 62} and means for the regulation of vapor concentration⁵² are in process of elaboration and trial.

Dust Suppression Consideration of the air as a vehicle of infection would be very incomplete without reference to the importance of dust, both as a carrier of pathogenic bacteria and viruses and as a shield of air-borne pathogens against the means used for disinfection of air, such as ultra-violet radiation and germicidal vapors. British investigators^{21, 36} in particular, working under wartime conditions, have found dust a very serious obstacle to application of measures for disinfection of air.

They have introduced practical methods for reducing dust from floors, textiles, and bed clothes by treatment with light paraffin oils

Results of practical trials of the effect of suppression of dust by oiling have recently been recorded²² Measles, a catarrhal disease, often complicated by hemolytic streptococcal infection, affords conditions in which a patient's surroundings are particularly apt to be contaminated by streptococci which remain viable and may readily be redispersed in dust

"An investigation into the control of dust-borne haemolytic streptococci was carried out in two measles wards of identical design during the spring of 1943 In the *Test Ward*, during a three-weeks preliminary period, the floor alone was oiled During a subsequent nine-weeks period bed-clothes, patients' garments, and all other woollen and cotton articles in ward use were treated regularly with emulsions of technical white oil, and the floor was re-oiled at intervals In the *Control Ward* no anti-dust measures were taken In both wards the air was sampled for total bacteria and for haemolytic streptococci during bed-making and sweeping, and the streptococcal cross-infection and complication rates were recorded and analysed In assessing the cross-infection rate Type 6 streptococcus was adopted as the 'indicator organism,' since in the two wards it accounted for 90 per cent of the cross-infections and for all the middle-ear complications occurring after admission

"In the *Test Ward*, while the floor alone was oiled the Type 6 cross-infection rate was 58.1 per cent, compared with a rate of 53.3 per cent in the *Control Ward* In each ward the middle-ear complication rate due to Type 6 was 18.4 per cent Haemolytic streptococci were numerous in the air of both wards during bed-making, the predominant strain being Type 6 Thus oiling of floors alone was not sufficient to control the spread of dust-borne haemolytic streptococci in measles wards

"In the *Test Ward*, while the full anti-dust measures of oiled bed-clothes, garments, etc., and oiled floor were in force (a) the mean haemolytic streptococcus count in the air during bed-making was reduced by 97.5 per cent, (b) the mean bacterial count in the air during bed-making was 91 per cent less, and the mean haemolytic streptococcus count 98 per cent less, than in the *Control Ward*, (c) the mean bacterial count in the air during sweeping was 92 per cent less, and the mean haemolytic streptococcus count 99 per cent less, than in the

Control Ward, (d) the Type 6 cross-infection rate was 18.6 per cent, while in the *Control Ward* it rose to 73.3 per cent, (e) the middle-ear complication rate due to Type 6 was 2.8 per cent, compared with 14.3 per cent in the *Control Ward*. Thus the oiling of all bed-clothes and ward-linen, in addition to the oiling of floors, effectively controlled dust-borne streptococcal infection in measles wards. Cross-infection from direct contact or mediate means was not prevented by anti-dust measures.

"A high streptococcal infection rate occurred in spite of intensive sulphonamide prophylaxis. The cross-infecting Type 6 strain was found by *in vitro* tests to be sulphonamide-resistant."

A complete and practical technique for the application of dust-laying oils to blankets, sheets and other woolen and cotton fabrics has been worked out in the laboratories of the British Launderer's Research Association.⁶³

In another British study⁶⁴ the wooden floors of all barrack-rooms, sleeping huts, offices and lecture-rooms in a military training center were treated with spindle oil at regular intervals. The floors of a similar unit were left untreated as a control. Careful weekly records were kept of all men reporting sick with a respiratory infection during the seventeen weeks ending March 27, 1943. The respiratory infection rate was 7 per 1,000 men in the unit with oiled floors, 38 per 1,000 in the control unit. The oil used was non-inflammable, caused no unpleasant smell and made the floors easier to keep clean. "The regimental officers and men welcomed the oiling of the floors."

Robertson and co-workers⁶⁵ have recently reviewed the literature on dust-suppressive measures in relation to cross-infections in hospitals and military establishments. Practical means and techniques are considered in detail. A test is reported on the effect of oiling floors and bed clothes on the incidence of acute respiratory diseases among 5,500 troops in the test barracks and a similar number in the control barracks over a ten weeks period. An average weekly reduction of 24 per cent in hospital admissions for respiratory disease was obtained in the treated barracks. In the test groups whose controls had a high rate of infection, average weekly reductions in hospital admissions of over 50 per cent and of dispensary visits for respiratory infections of 37 per cent, were obtained.

Experiments on the reduction of the infectivity of dust by floor irradiation with ultra-violet have been instituted by Hollaender, du

Buy, Ingraham, and Wheeler⁶⁶ As a result of these experiments they suggest that "floor irradiation be combined with ceiling irradiation in practical tests in barracks or hospital wards to determine the effect of any ultra-violet irradiation in lowering morbidity rates or preventing cross-infection " They caution that "if such experiments be attempted it must be borne in mind that certain types of flooring may prove to be capable of reflecting sufficient amounts of ultra-violet to cause harmful effects "

Thus rationale and scientific basis have already been laid down for three independent types of measures for controlling the dissemination of disease agents through the air—ultra-violet irradiation, germicidal vapors and dust suppressive measures Each has been shown capable, under appropriate conditions, of reducing significantly the incidence of respiratory infection Doubtless all of these measures, singly and in combination, will find their places in the maturing practical art of air sanitation

Studies directed primarily against the secondary reservoirs of infection in floor dust, the lint of bed clothes, etc , have for the most part used the dissemination of hemolytic streptococci as a primary criterion These disease agents, because of their chain structure, are quick to settle out of the air, and they remain viable for extended periods The use of hemolytic streptococci as indices, therefore, may tend to overemphasize the relative importance of dust and underemphasize the importance of droplet nuclei in the over-all picture of air-borne infection

A recent study⁶⁷ of the seasonal patterns of certain infectious diseases indicates that methods directed against air-borne "droplet nuclei" and those directed against the secondary reservoirs of pathogens may have quite different values in respect to the suppression of different disease agents The author concludes

"The seasonal patterns of spread of measles and chicken pox, while differing markedly from each other, are both entirely compatible with the theory, outlined at the beginning of this paper, of transmission by air-borne droplet nuclei

"The seasonal patterns of scarlet fever, on the other hand, suggest that means of transmission less amenable to control by ventilation than are droplet nuclei play an important role in its spread "

In the total problem of control of respiratory disease, of course appropriate measures for immunization of individuals and groups, and

the emerging technique of chemoprophylaxis,^{68 72} are as important as measures of environmental sanitation. However, immunization and chemoprophylaxis are outside the scope of this review.

Considered in terms of cost in money and effort when applied on a national scale, control of air-borne infection seems to present a problem of very great proportions. Relative to what it costs to leave air-borne infection uncontrolled, however, the money costs of preventive measures shrink to comparatively trivial figures. Is the effort too much to ask of a people whose energies have so long been mobilized for the purposes of war? Is not a part of any rational program of reconversion to peace the clear conception of orienting purposes whose achievement would add to national health and well-being? Is not freedom from sickness worthy of a place with freedom of worship, freedom of speech, freedom from want, freedom from fear?

SUMMARY

Respiratory disease is responsible for more than a third of the total number of person-days lost to American industry by disability, it is of course a correspondingly serious problem in domestic life and during military training. The air of enclosed spaces is at present the principal vehicle for the dissemination of respiratory disease. The rationale of rendering air safe for human occupancy has been laid down in the laboratory and in suitable, controlled human environments. The means are ultra-violet irradiation, dust-suppressive measures, and the use of germicidal vapors of hypochlorous acid and of propylene and triethylene glycol. Elaboration of the practical art of providing safe air supplies is, however, not to be accomplished cheaply or through the efforts of a few people. A specialty or specialties in sanitary engineering will have to develop around air sanitation, as has occurred around water and milk sanitation. Physicians, air-conditioning specialists, heating, ventilating, and illuminating engineers, architects, the manufacturers of necessary equipment, agencies regulating public health practice, and the industries which will benefit by reduction of industrial disability through respiratory disease ultimately will all have to contribute effort and money to solving the manifold aspects of the problem. How much is it worth in war time to reduce an annual industrial waste equivalent to the output for a year of approximately a half million workers? How much is it worth in peace time to reduce a corresponding loss of effi-

ciency and well being from the drain of respiratory infection³

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EXPERIENCES WITH RHEUMATIC FEVER
IN THE ARMY *

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AN attempt to crystallize the status of experience with rheumatic fever at this time is fraught with hazard, yet such attempts seem warranted even if their main function remains but to challenge previous conceptions and to raise new questions. The opinions expressed in this paper are those of the author and are not shared by all workers in this field. They are not to be construed as representing official pronouncements of the Office of The Surgeon General.

Rheumatic fever, as most physicians knew it prior to the war, was largely an endemic disease with sporadic, but relatively rare epidemics of minor proportions. It was not considered to be highly communicable. Numerous publications contended that the major etiological factors were malnutrition, poor heating, and other problems of the underprivileged classes. By far, the majority of cases developed in children and adolescents. It has always been a potentially very serious disease for the affected patient.

It is a serious problem for the military forces, both because of the immediate long hospitalization and because of the danger of the effects which may invalid these patients for years later in life. In several areas it has assumed epidemic proportions. These have been most pronounced in camps in the Rocky Mountain and Central states. In some barracks it has reached a much higher incidence than would have been anticipated in this age group, on the basis of former experience.

The curve of incidence has, in general, diminished with increasing age. The oldest patient seen by the author, having his first attack while in an Army hospital, was 42 years of age.

The military personnel with this disease have not been emaciated, undernourished, or in poor physical condition. On the contrary, they represent, in most instances, the cream of our youth, physically and

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mentally They are in splendid physical training Those stricken in this country have been on plentiful diets which were, for the most part, very well planned Some of the men who developed rheumatic fever overseas have been on field rations for from one to five months Heavy physical exercise with resulting fatigue has been frequent, but not invariable before onset Exposure to prolonged dampness and cold has appeared to precipitate many attacks, but again has not been an invariable prefatory occurrence

Close contact in living quarters has been a most consistent environmental factor, as it almost invariably must be, in the spread of the disease since practically all attacks of rheumatic fever are preceded by Group A hemolytic streptococcal infections of the respiratory tract Evidence is increasing that the lesions of rheumatic fever may be the results of an anaphylactic reaction to some foreign antigen, such as a product of the hemolytic streptococcus^{1,2} This applies to the reaction of rheumatic pneumonitis³ as well as joint and skin manifestations

Characteristically, in the Army camps the curve of increase in the incidence of rheumatic fever has been preceded by a curve of increased incidence of upper respiratory infections Where bacteriological studies have been made, these have been predominantly Group A *Streptococcus* infections On the other hand, many waves of upper respiratory infections have not been followed by any increase in rheumatic fever This has been previously observed in relation to the Autumnal epidemics of "colds" along the Eastern seaboard

In general, the Army cases have followed the usual course of events as outlined by Swift⁴ namely

Phase I—An upper respiratory streptococcal infection, either a nasopharyngitis, follicular tonsillitis, or scarlet fever

Phase II—A quiescent phase, which may be considered as an incubation period, and

Phase III—The phase of rheumatic activity, which may continue in duration from a few weeks to years

Actually the first two phases frequently escape detection, or are quickly forgotten, so that only careful questioning will reveal even an approximately accurate rate of incidence These two phases are, nevertheless, of greatest importance since most patients convalescing from *streptococcus* tonsillitis, or nasopharyngitis are below par physically, and being candidates for rheumatic fever and other serious diseases

should not be exposed at too early a date to too great cold, dampness, or fatigue

The second phase may pass immediately into the third or active rheumatic fever phase, or it may take as long as six to seven weeks. Most of the serious complications can be detected by having the patients under observation between the fifteenth and twentieth days after the onset of Phase I. In military establishments this is not always feasible, but proper instructions can be issued to the soldier so that suspicious symptoms or signs developing during that time will be brought immediately to the attention of the medical officer.

The history of previous attacks has been very common. In one ward in an Induction Center Station Hospital of twenty-eight patients who had developed rheumatic fever within thirty days of their entrance into the service, eighteen had had a previous history of one or more previous attacks from one to fourteen years before. Most of these men had done fairly well in the protected environment of civilian life, but even a brief trial with exercise and exposure to which they were unaccustomed resulted in reactivation of their disease. Ten of them had no history suggestive of the first phase of upper respiratory infection.

This gives rise to the following question: Is this new attack, thus precipitated, due to hidden foci of streptococci Group A, or is it due to reactivation of a latent anaphylactic process secondary to the stimuli of fatigue, exposure to inclement weather, or upper respiratory infections, any one of which may act as the trigger mechanism initiating the process?

It has been difficult, and even impossible at times, to differentiate the pseudo from the true rheumatic fever syndrome. The confusing signs include tachycardia, substernal distress, dyspnea on exertion, pronounced arthralgia, and backache, without local redness, heat, or swelling of the soft parts. If not due to true rheumatic fever, these are usually considered to be on the basis of toxicity (though we do not know exactly what we mean by that term), and disappear with the general improvement of the patient.

Most of the patients in the military services have followed the usual course during the active rheumatic fever phase. Several points, however, are worthy of note. In more than 1000 patients, there have been only three who have had chorea at any time, during their Army serv-

ices In no case has it occurred as an isolated manifestation of rheumatic fever This is remarkably lower than the incidence of chorea in rheumatic fever in pre-war civilian practice

The characteristic painful, swollen, red, hot joints have varied greatly in shifting tendencies and in severity The cardiac manifestations have included precordial discomfort, tenderness on pressure, pain, dyspnea, tachycardia, premature contractions, fibrillation, and flutter. Heart block varied from partial to complete with ventricular rates as low as 20 per minute This will be discussed later in this paper

The hearts have rarely been slightly enlarged with the first attack On auscultation the first sign of change has most frequently been a muffled soft *systolic blowing murmur* over the mitral area with a fairly wide distribution This has frequently disappeared on change of position such as sitting upright, and may disappear completely with subsidence of the acute phase of the disease, in which case it may be difficult to be certain whether it was evidence of an organic or functional process Although the fashion of the day is to arbitrarily classify many such murmurs as functional, it would seem advisable to be less positive since the post-mortem findings have embarrassed the clinician more than once in this regard *Diastolic* and *presystolic* murmurs in this area are more safely classified as organic In some instances, a *mid-diastolic rumbling murmur* has developed two to three months after the initial rheumatic fever attack Several of these have later become inaudible The explanation for this is not clear The most common *murmur in the aortic area* has been soft, blowing, and *diastolic* heard loudest over the second and third right interspace It probably represents a relative insufficiency in the majority of patients and frequently, but not always, disappears The murmurs of mitral and aortic stenosis tend to develop later, and were with few exceptions, encountered only in patients with previous history or evidence of rheumatic fever

Pericarditis, while not common, has occurred frequently enough to be worthy of constant consideration Most of these patients developed their pericardial signs within a few days of the onset of the active rheumatic fever phase, often before therapy had reached an intensive phase The lack of reliability of statistical studies in this regard was recently brought forcibly to my attention by the following incident—Two hospitals drawing from the same pool of personnel each had approximately seventy-five patients with rheumatic fever One had no

patients with pericarditis, the other had eight patients with pericarditis. In each of these the pericarditis developed within the first four to five days of onset of recognized rheumatic fever.

Heart failure has been very rare during the first attack, having been encountered in only five patients in this series. Changes in the electrocardiogram will be discussed below.

It must never be forgotten that abdominal symptoms may represent the onset of rheumatic fever. Pain, tenderness, rebound tenderness, and cramps have been frequent and have led to confusion with the diagnosis of appendicitis.

Of particular note has been the scarcity of subcutaneous nodules—only four examples have been seen in more than 1000 cases. Purpura has been rare. The reason for this is not understood. Of possible significance in this regard is the recent work of Link⁵ and others demonstrating that salicylates may produce hemorrhage. This occurs only in the presence of a Vitamin K deficiency and is prevented by adequate Vitamin K in the diet. This may, in part, explain the tendency toward hemorrhage noted in underprivileged children and its absence among well nourished troops. It has further been noted⁵ that sodium salicylate, which is used in the Army, produces less tendency toward reduction of the prothrombin level than acetyl salicylic acid—commonly used in civilian practice.

We have seen eight examples of cerebral manifestations, five simulating meningitis and three developing a transient psychosis. In these three the question of salicylism was considered. In this series, there have been seven fatalities. Two were associated with pericarditis, and five with heart failure. All of these had histories of previous attacks of rheumatic fever. Four of the latter five had pneumonia which, in two instances, was shown pathologically to resemble rheumatic pneumonitis as described by Rich and Gregory.³ Numerous additional patients developed what was diagnosed as primary atypical pneumonia, but which was probably in some cases, rheumatic pneumonitis. This possibility should be constantly kept in mind in treating patients with rheumatic fever.

Electrocardiographic changes have been of great interest. The most consistent change was prolongation of the P-R interval—the longest seen being 0.62. This finding is often the only evidence of heart involvement and is usually transient, disappearing in from one to six

months Partial A-V heart block with the Wenckebach phenomenon and dropped beats has occurred in approximately 6 per cent of the cases Auricular ventricular dissociation has occurred with equal frequency

Prolongation of the P-R interval was found in fifteen out of two hundred patients suffering from what was considered to be typical rheumatoid arthritis, at the Army and Navy General Hospital Aschoff bodies have been found in the hearts of many patients who died after years of so-called typical rheumatoid arthritis The prolonged P-R intervals added additional evidence to the hypothesis that, in many instances, these diseases are closely related or run concurrently in susceptible individuals

The question inevitably arises as to whether we are detecting all of the changes which takes place in the heart Wendkos⁶ has contributed suggestive information to this field by the following study Eight men suffering from acute migratory polyarthritis (typical of rheumatic fever), in whom no evidence of heart damage existed, showed normal electrocardiographic tracings Immediately after a controlled tracing, 0.5 Mgm of ergotamine tartrate (a sympatholytic drug) was injected intravenously in each Further tracings were recorded thirty and sixty minutes after injection Additional tracings were taken of five patients after all evidence of activity of the disease had subsided The results were as follows The control tracings in each instance were normal In six of the eight cases the tracings taken after the injection of ergotamine showed significant disturbances in rhythm usually associated with rheumatic fever, consisting of first degree A-V heart block in four instances, second degree A-V heart block with dropped beats in one instance and nodal rhythm with first degree A-V block in another The maximum effect was noted in thirty minutes and the effects had generally disappeared within sixty minutes In the five individuals, who were rechecked after the active phase of the disease had subsided, no alterations from normal, except for slight slowing of the sinus rate could be produced by the same experiment They had returned to the state of reactivity which characterized normal hearts checked by this method

If this work is substantiated by additional studies, it would appear to offer a means of sensitizing our technique for the detection of cardiac involvement in rheumatic fever We do not as yet know whether other

TABLE I (From Wendkos)

CHANGES IN THE ELECTROCARDIOGRAM FOLLOWING THE
ADMINISTRATION OF ERGOTAMINE

<i>Case No</i>	<i>Age</i>	<i>Date</i>	<i>Response to Ergotamine</i>	<i>Remarks</i>
1	24	2-14-44	Second degree A-V heart block with dropped beats	Rapid sedimentation time Joint pains present
1	24	3-25-44	Some slowing of sinus rate	Normal sedimentation time Joint pains absent
2	21	1-24-44	Nodal rhythm with first degree A-V heart block	Rapid sedimentation time Acute polyarthritis
2	21	3-1-44	Some slowing of sinus rate	Normal sedimentation time Joint pains absent
3	19	12-10-43	First degree A-V heart block (PR-0.28)	Rapid sedimentation time Acute polyarthritis
3	19	3-10-43	Some slowing of sinus rate	Normal sedimentation time Joint symptoms absent
4	21	3-12-44	First degree A-V heart block (PR-0.40)	Rapid sedimentation time Joint pains both shoulders
4	21	3-23-44	Some slowing of sinus rate	Sedimentation time reduced Joint pains absent
5	19	3-12-44	First degree A-V heart block (PR-0.32)	Acute polyarthritis Sedimentation time rapid
5	19	3-18-44	Some slowing of sinus rate	Arthritis completely disappeared Sedimentation time reduced
6	34	1-3-44	First degree A-V heart block (PR-0.30)	Sedimentation time rapid Acute polyarthritis with some persistent deformity and swelling in small joints of hand

infectious diseases can produce a similar reaction, or whether such a reaction can be elicited during the toxic period of the first, or upper respiratory phase of rheumatic fever

It has previously been demonstrated that a parasympatholytic drug such as atropine can temporarily abolish the first degree A-V heart block and other types of rhythm disturbances, which are the chief electrocardiographic expressions of the disease. This work with ergotamine tartrate suggests that subordination of a hypervagotonic state below a critical level will prevent the registration of the usual electrocardiographic pattern of this dysfunction. The depression of the normal antagonist of the vagus by the use of a sympatholytic preparation

such as ergotamine tartrate may permit the latent phase to register existing changes in the electrocardiogram. Further studies of this phenomenon may yield worthwhile information and aid us to evaluate more accurately the extent of involvement of the heart during the acute phase of the disease. The degree of *permanent* damage in mild cases still eludes our best efforts.

Other transient changes in the electrocardiogram have been frequently observed. These include inversion of the QRS complex and diminution or inversion of the T wave, especially in lead 4. Serial electrocardiographic studies revealing elevation of all or most of the S-T segment, followed by inversion of T waves in multiple leads have been suggestive of pericarditis with an active inflammatory process in the subepicardium. In 18 per cent of a series upright T waves exceeding 10 Mm occurred in lead CF₄.⁷ Wandering pacemakers were encountered in a small number of cases.

THE CHEMOTHERAPEUTIC ASPECTS OF THE TREATMENT OF RHEUMATIC FEVER

While no completely satisfactory therapy is available for rheumatic fever, the attack has been actively pressed in the military hospitals. Penicillin is now recognized to be of no value in combating this disease.^{8,9} The therapeutic use of the sulfonamides has likewise been disappointing. The prophylactic use of sulfonamides will be discussed below. The streptococcus antisera have been without value.

The most interesting contributions to therapy have dealt with the use of salicylates, which have entertained varying degrees of popularity during the past years. A very definite step forward was taken by Brodie, Udenfriend and Coburn in establishing a method for determining the level of salicylic acid in the plasma.¹⁰ This at least makes it possible to be certain that adequate absorption takes place by whatever method of administration is used. While there may be some correlation between the level of salicylates in the plasma and the therapeutic response, there is a considerable variation in this which may be due to (a) a difference in response of the antigen or the inflammatory reaction in different hosts, (b) to the possibility that the level in the blood may not always bear a direct relationship to the level, or utilization in the affected tissues themselves. Further work will help to clarify this point.

The use of larger doses of salicylates orally and intravenously has

been advocated by Coburn and others. This has stimulated more careful observations of the use of these large doses and certain facts and questions have evolved. We have found that most of our patients can tolerate, without serious inconveniences, doses of salicylates which we formerly hesitated to prescribe. A dose of 6 to 8 grams daily was formerly considered to be a large dose. Coburn suggested 10 gms (150 grs) as an average, seeking to maintain a level of 35 mg per 100 cc or higher. I have seen 20 gms (300 grs) given daily to certain patients without detectable untoward effects. Perhaps this tolerance for the drug is related to the splendid physical condition of the men at the onset of the disease and to the diets which they have received containing adequate vitamin K. At present, this must remain speculation. The problems of salicylism will be discussed later.

Agreement has been reached regarding the value of salicylates administered orally, but the determination of additional value following intravenous administration is still debated. The action of salicylates is, in all probability, not upon the infectious agent but rather upon the sterile inflammatory reaction which occurs during activity of the rheumatic process. The evaluation of therapeutic response is determined by clinical improvement and the curve of the sedimentation rate which is generally accepted as being of great value in following the course of this disease.

Early reports suggested that the administration of 10 gms of sodium salicylate per day intravenously for 6 to 8 days followed by the oral administration of equal doses would result in a rapid subsidence of clinical activity and a drop in the sedimentation rate to within normal within fourteen days. Most of our patients have responded very well clinically to rest in bed and from 10 to 12 gms of salicylate daily without intravenous therapy.

The evidence at present seems to indicate that intravenous administration has no advantages over oral administration, with the possible exception of rapidity of rise in the blood level. If this route is to be used at all, salicylates should be given intravenously only to very acutely ill patients and patients with evidence of early pericarditis. There is considerable doubt that it is ever necessary.

The response of the sedimentation rate to both intravenous and massive oral dosage has been disappointing having, in a large proportion of our patients, failed to approach normal until the third to the

sixth week of the treatment This lag has occurred in spite of blood levels of 35 mg per 100 cc or more

The use of the large dose technique with blood levels of 35 mg or higher does not offer complete protection against pericarditis I have seen four patients who developed pericarditis during intravenous therapy

Comparable series were studied in one hospital with the intravenous technique (10 gms daily) followed by 10 to 16 gms orally of sodium salicylate daily and with oral administration alone

Of twenty-nine patients treated initially by intravenous technique, six had probable or definite heart disease before this attack (based on a history of rheumatic fever and presence of a cardiac lesion) Twenty developed evidence of a cardiac lesion during the period of observation as judged by either progressive electrocardiographic changes or the development of what were considered to be significant murmurs Nine did not Five of the new patients showed persistent evidence of cardiac residua in the form of significant murmurs Eleven showed no residua On thirteen, the late follow-up was unsatisfactory

Of twenty-nine patients treated throughout by oral administration of 10 gms daily, seven had cardiac disease before the present attack, eighteen developed signs during this episode, five of these showed persistent cardiac residua, nineteen showed none, and on five, the follow-up was unsatisfactory In reference to cardiac lesions, the results were, therefore, not strikingly different in these small series

While there exists serious doubt regarding the merits of intravenous over oral methods of administration, there is practically universal agreement that massive dosage (10 gms or more) given by either route has produced more uniformly satisfactory palliative results than the smaller doses formerly employed Many patients can be cited in whom the clinical course including the sedimentation rate improved strikingly with elevation of the plasma salicylate level but in whom the relapses occurred when the plasma level was allowed to drop below 20 mg per 100 cc Sharp evidence that this problem is far from solved was presented by one series of sixty-four patients receiving massive dosage therapy by mouth of whom twenty-nine or 45 per cent developed persistent valvular heart lesions

One of the complications which has been more prominent following the use of such large doses of salicylates is acute salicylism Some patients

can tolerate levels of 60 mg per 100 cc without symptoms but many of our patients develop mild symptoms at a level between 25 and 35 mg, and the percentage increases with the elevation of the level. Beginning with tinnitus, colored vision, nausea, and vomiting, this may progress to a more severe phase of which hyperventilation is a warning signal. This may increase in depth and intensity to simulate Kussmaul breathing. This hyperpnea produces a respiratory (paradoxical) alkalosis which results in lowered CO_2 content of the serum, loss of base (sodium) from the serum via the urine, retention of chloride in the serum, decreased renal function with retention of water, numbness, tingling of extremities, and tetany with carpopedal spasm and positive Chvostek's sign. An acute maniacal delirium may accompany this picture or develop as an isolated reaction.

Mild or moderate salicylism is not of serious significance. If severe with a serum salicylate level of under 50 mg per 100 cc, one or two liters of normal saline intravenously with sodium bicarbonate, 0.6 gms every four hours by mouth is usually adequate. If the level is over 50 mg the salicylate should be stopped and one to five liters of normal saline given intravenously slowly. This toxicity can be prevented in practically all cases by a dose of 0.9 gms of sodium bicarbonate with each dose of salicylate.¹¹ On the other hand, it has been shown by Smull, Wégria, and Leland,¹² that the administration of therapeutically satisfactory doses of sodium bicarbonate definitely decreases the level of salicylates in the blood. We must apparently, by balancing the administration of these two substances, tread between the maximum therapeutic effect and the toxic level, and this zone may differ considerably in different individuals.

For the reasons presented above, salicylic acid cannot be considered the final solution to the therapeutic problems occurring in rheumatic fever. The objectives can be clearly stated. A drug must be found which 1) is non-toxic in effective therapeutic doses, 2) modifies the immune response of the host so that the patient recovers promptly after a monocyclic attack, or 3) inhibits the capacity of the infecting micro-organism to elaborate antigen. In the absence of fulfillment of any of these objectives we are limited at present to the action of the salicylates in suppression of the inflammatory process.

The possibility of prophylaxis of rheumatic fever with sulfonamides has been the subject of much thought and study. These drugs are of no

value in the treatment of the acute phase of the disease. Figures have been presented on numerous occasions supporting the thesis that small doses of sulfanilamide (0.5-1.0 gm.) taken daily will markedly decrease the incidence of recurrences of rheumatic fever after the first attack. Statistically, some of these figures have been subject to question.

Some of the patients have now taken this dosage for several years. This interminable program is not feasible as a preventive measure for use with groups of thousands of troops merely because they happen to be located in an area with a high rate for rheumatic fever. Methods have been used whereby varying dosages have been administered, i.e., 4 gms sulfadiazine in 48 hours, 6 gms in 72 hours, and 1 gram daily for a period of weeks. The rates of upper respiratory diseases can apparently be very favorably affected,¹³ especially by the last named dose. This can be anticipated in those that are associated with streptococcus infections.

Scarlet fever and meningococcus infections are likewise favorably affected by the sulfonamides prophylactically. The evidence for the long-term effect on rheumatic fever of these small doses over short intervals is to date suggestive,¹⁴ but less conclusive and must await further work.

Fear has been expressed that the early use of sulfonamides after the acute phase of rheumatic fever might unfavorably affect the course of the disease even causing relapses. Under our direction one gram of sulfadiazine has been given to each of twenty-five patients daily for twenty-one days beginning on the fifth day after the temperature had reached normal, regardless of the level of the sedimentation rate. In no instance was any elevation of the sedimentation rate or change in symptomatology noted which could be attributed to the administration of the sulfadiazine, therefore, although the possibility cannot be denied, it seems that risk on this basis is probably not excessive. Further studies on this problem are being carried out. The risk of sulfonamide sensitization must be considered in mass treatment. After sensitization has occurred, skin reactions are not uncommon and we have seen two acute deaths which appeared to be of an anaphylactic nature.

COMMENTS AND CONCLUSIONS

Rheumatic fever, as it occurs in the Army, has been demonstrated to be a manifestation of a highly communicable disease complex which

frequently is preceded by an outbreak of upper respiratory infections. Evidence is accumulating that it is an anaphylactic reaction, probably to the streptococcus Group A. This is not, however, conclusively established as yet. It may be widespread in its attack on well-nourished young men believed to be in excellent physical condition. The greatest involvement has been among the *younger groups* of servicemen. Fatigue, exposure to cold and dampness, and close living quarters are believed to be important environmental factors. Patients with a previous history of rheumatic fever are especially susceptible to recurrences when exposed to the rigors of military life.

The symptoms, physical findings, laboratory and electrocardiographic changes have been presented. The rarity of subcutaneous nodules, purpura, and chorea is of especial interest. The occurrence of prolongation of the P-R interval and of Aschoff bodies in the hearts of patients with "so-called" typical rheumatoid arthritis of many years standing has been confirmed. The possibility of sensitizing our methods of determining latent damage to the conduction mechanism of the heart by the use of ergotamine tartrate has been discussed.

The present status of the treatment of rheumatic fever remains unsatisfactory. Penicillin and the sulfonamides have been proven to be valueless in the treatment of this disease. There is no evidence that penicillin is of value as a preventive. Prolonged daily dosage of sulfanilamide appears to lessen the frequency of recurrences¹⁴. The evidence that short courses of sulfonamides are of long term value in the prophylaxis of primary or recurrent attacks of rheumatic fever is suggestive, but not as yet conclusively established. It is possible to markedly reduce the rate of upper respiratory infections, especially those associated with certain strains of streptococci by this method.

A step forward has been taken in the treatment of rheumatic fever with the development of a method for determining the level of salicylates in the blood thus aiding in the control of the dosage. It is fairly well agreed that large doses of sodium salicylate, i.e., 10 gm daily or more are more rapidly palliative than the formerly used smaller doses. It is highly doubtful that the intravenous administration of salicylates is of greater value than oral administration. The clinical response to large doses has been rapid but the response of the sedimentation rate has in many of our cases been disappointingly slow. The use of the massive dose methods does not offer complete protection against pericarditis,

myocarditis, or endocarditis

With massive doses salicylism must be watched for. It can be prevented by giving sodium bicarbonate with the sodium salicylate, but it should be appreciated that this will result in a lowering of the blood level of the salicylates. The effect which this may have on the efficiency of the salicylates has not been established.

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CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

MAY 16, 1945

MEDICAL DIVISION

BERNARD S. OPPENHEIMER, *Chairman*

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Electrocardiographic Changes During Intravenous Therapy of Pneumonia

DAVID D. RUTSTEIN, K. JEFFERSON THOMSON and DANIEL M. TOLMACH

Evidence has previously been published* that certain reactions to the intravenous administration of antipneumococcus serum are not due to anaphylaxis but are a response of the circulatory system to reaction-producing materials contained in the preparation of serum used.

As an outgrowth of this study, an investigation was performed on the changes in the electrocardiogram occurring during the intravenous administration of antipneumococcus serum and the sodium salts of the sulfonamide drugs.

Significant electrocardiograph changes occurred in 16 of the 112 injections of

antipneumococcus serum in 59 pneumonia patients and in 3 of the 32 injections of sodium salts of sulfonamide drugs in 24 pneumonia patients.

Striking changes occurred in serial electrocardiograms in 3 patients, in one of which the changes are indistinguishable from those associated with acute myocardial infarction and 2 of which are suggestive of severe myocardial damage. One of these patients received Type 1 antipneumococcus horse serum, another Type 8 antipneumococcus rabbit serum, and the third sodium sulfathiazole.

* "Immediate Serum Reactions in Man," Archives of Internal Medicine Vol. 68 pp. 25-56, July 1941.

* * *

Streptomycin in the Treatment of Typhoid Fever

HOBART A. REIMANN, ALISON H. PRICE and

WILLIAM F. ELIAS, Ph.D.*

From the Jefferson Medical College and Hospital, Philadelphia

Streptomycin, an antibiotic substance derived from *Actinomyces griseus*, is bactericidal for *E. typhosa* in amounts of 4 to 6 units per cc. of broth. These amounts can be easily attained or exceeded in the body by intramuscular or intravenous injection of from 1 to 4 million units daily; they can also be attained in the stool by oral administration of similar amounts.

Five patients with typhoid fever were treated: 3 intramuscularly, 1 intravenously and in 1 both orally and intravenously. They received from 9 million to 30 million

units. No beneficial effect occurred in 1, but recovery accompanied therapy in 3. In another patient treated intravenously, the temperature was falling when the supply of streptomycin was exhausted. The temperature rose to high levels again.

Streptomycin can be attained in the body in amounts which are theoretically adequate to kill *E. typhosa*. In 5 treated patients, recovery was synchronous with therapy in 3. There is reason to believe that the drug will also be of value in infections caused by other pathogenic gram-negative bacilli.

* From the Wyeth Institute of Applied Biochemistry, Philadelphia.

*The Clinical Response in General Paresis to Treatment with Penicillin**†

EDWIN J DOTY, HERBERT KOTEEN and WALSH McDERMOTT

In a series of 115 neurosyphilitics who were treated with penicillin, only eight patients presented unequivocal evidence of general paresis. Satisfactory therapeutic results, as judged by physical, psychiatric and laboratory examinations, were observed in four of the eight patients during a follow-up of six to twelve months. With one exception, the observed improvement was not so marked as is usually seen at a comparable interval after malaria therapy. Two

patients with advanced paresis failed to improve after 9,000,000 and 18,000,000 units of penicillin, respectively.

The results of this preliminary study would indicate that although intensive penicillin therapy exerts a definite beneficial effect on the mental, physical and laboratory abnormalities of general paresis, the extent of this beneficial effect, at least with the present dosage, is not so satisfactory as that following malaria.

* From The New York Hospital, and the Departments of Medicine and Psychiatry, Cornell University Medical College, New York.

† Work done under contract with the Office of Scientific Research and Development.

* * *

Objective and Clinical Study of the Normal, Desquamated and Atrophic Tongues

JOSEPH R. DiPALMA

The purpose of this study is to place upon an objective basis the clinical observation of changes in surface contour of the tongue in certain diseases, particularly the anemias and the avitaminoses.

By the development of a special ink which is tasteless, non-poisonous, of the proper consistency, and fast drying, it has been possible to make accurate prints of the tongue. When studied under the low power microscope it is possible to not only count the relative populations of the filiform and fungiform papillae but also to make observations on the surface contour of the mucous membrane of the tongue. Study of over 100 normal adults in the third decade of life has established the average surface contour and papillae count of the normal tongue.

Comparison of the normal tongue prints with those in disease conditions has revealed the following. People with a poor dietary history show a marked tendency to desquamation of the filiform papillae, especially with acute systemic infections such as pneumonia. However, the underlying

fungiform papillary structure remains intact. Recovery quickly takes place with vitamin therapy. In advanced avitaminosis and in senile atrophy of the tongue both filiform and fungiform papillary structure disappears. Recovery, if it occurs at all, is very slow.

In the anemia group, pernicious anemia is distinctive because of the tendency of the tongue to show longitudinal ridging during the relapse, the so-called "scrotal pattern." The hypochromic anemias, when severe, show the most marked flattening of surface pattern. Even in these tongues recovery can be demonstrated with specific therapy of the anemia and with vitamins.

On the basis of these observations a plea is made for modification of the clinical term, "the smooth tongue." While this term is descriptive it fails to indicate exactly the change in surface contour. By the simple method here described it is possible to state accurately that the tongue is either just desquamating or is going on to atrophy of papillary structure.

The Modified Insulin Technique in the Treatment of Ambulant Psychiatric Patients

RICHARD M. BRICKNER

1 The ambulant insulin treatment method of Polatin, Spotnitz and Wiesel has been employed in 26 cases of different types

2 The symptom of intense tension can usually be relieved, in whole or in part, by this treatment.

3 This series also adds a small amount of evidence to that more extensively accumulated by others, that the basic illness may be relieved by this method. This applies to schizophrenia and to depression.

4 The treatment may be given either in occasional isolated doses or as a systematic procedure with increasing doses, extending over a period of weeks.

5 The treatment is feasible for office use. After the injection has been given, no special set-up is required beyond the presence of a trained person to watch the patient and the presence of the doctor in the office.

6 The dosage ranges are far lower with the subcutaneous than with the intravenous route of administration.

7 The treatment cannot be used in the office with psychotic patients unless the manifestations are symptomatically mild. Patients should be hospitalized instead, if there is any question of risk in keeping them unhospitalized.

* * *

Personality Reaction to Crime and Disease

DAVID ABRAHAMSEN

Research Associate, Department of Psychiatry, Columbia University

This psychosomatic study, supported by the Josiah Macy Jr. Foundation, is a preliminary report of a clinical research project about the individual's personality reaction to his diseases and to his antisocial acts. Various types of conflicts may in due time lead an individual either into neurosis, psychosis, a psychosomatic disorder, or a criminal act. The question then is, *how* does a person react to his disease, and to an antisocial act of his own commission? The personality make-up present in the person determines how he will react when affected with a bodily disease and what form a maladjustment will assume. As the reaction to the illness depends upon what the personality was before the onset, so also the individual's reaction to his antisocial act is dependent upon his personality

traits before the antisocial act was committed.

From a group of offenders, two typical ones are selected for detailed description. Both experienced a childhood with deprivations, during adolescence they went through prolonged periods of physical ailments which seemed to be tied up with their personality traits and with their antisocial acts. Results of physical examinations and laboratory tests are given. Conclusions are drawn as to presence and incidence of some factors in the etiology of the individual's antisocial behavior and the nature and course of his disease and compared with the incidence of psychosomatic disorders in patients suffering from neurosis or psychosis.

A Comparison of Several Special Preparations of Protamine Zinc Insulin in the Treatment of Diabetes Mellitus

HENRY DOLGER

Twenty-five patients with severe diabetes mellitus who had been treated more or less satisfactorily with extemporaneous mixtures of insulin and protamine zinc insulin were studied. They were given three different fixed modifications of protamine zinc insulin specially prepared by the Research Laboratories of the Eli Lilly Company. Two modifications were acid clear and contained either 1.25 or 1.75 mgs of protamine per 100 units. The third was neutral (cloudy) and contained 0.42 mgs protamine per 100 units or one-third that found in commercially available protamine zinc insulin (i.e. 1.25 mgs). The latter, therefore, resembled

a mixture of two parts regular to one part protamine zinc insulin prepared extemporaneously.

The acid preparations were found to be similar to globin insulin in that late afternoon hypoglycemic reactions and severe early morning glycosuria were noted. The neutral preparation was more satisfactory by providing a smooth control of glycosuria and freedom from both afternoon and early morning insulin shocks. In fact this modification afforded even better results than the original extemporaneously prepared mixtures.

* * *

On the Significance of Nutritional Deficiency in Diabetes

MORTON S BISKIND and HERBERT SCHREIER

From the Endocrine and Diabetic Clinics, Beth Israel Hospital and the Diabetic Clinic, Gouverneur Hospital

Soskin and his collaborators,¹ in a brilliant series of investigations, have demonstrated the basic role of the liver in maintaining normal carbohydrate balance and have supplied abundant evidence that diabetes may often be a disease of the liver. Among other experiments, they have shown that damage to the liver by toxic agents produces the diabetic type of dextrose tolerance curve. It is now well known, through the work of many investigators, that nutritional factors, especially those of the B complex, protect the liver from both the functional and structural impairment which results from a variety of toxic agents; it has also been shown that the hepatic impairment which occurs from the latter, results from a secondarily-induced deficiency of the nutritional factors.

Among the functional impairments which result in the liver from primary or secondary deficiency of the vitamin B complex, is the failure of inactivation of estrogen,²

with the production of clinical syndromes associated with excess estrogen (menometrorrhagia, cystic mastitis, premenstrual tension, uterine myomas, postpartum subinvolution of the uterus, etc). Thus, a series of conditions, thought formerly to be purely endocrine, have been shown to result from impairment of hepatic function on a nutritional basis.³ Nutritional therapy in these conditions has produced striking improvement.

On the basis of these and related findings, for more than two years we have been investigating the occurrence of nutritional deficiency in diabetics, and on the basis of past experience in treating other syndromes related to hepatic dysfunction, we have studied the results of intensive therapy with the vitamin B complex in these patients. We have been impressed by the virtually universal occurrence of signs and symptoms of nutritional deficiency in diabetics, by the striking improvement in

general health and well-being which occurs on adequate oral or oral and parenteral vitamin B complex therapy, and by definite improvement in carbohydrate metabolism, often permitting a reduction in the insulin requirement, or its elimination altogether. In addition, patients requiring insulin had less difficulty with insulin reactions. In several cases in which marked improvement occurred with B complex, a definite correlation was possible between the occurrence of the hepatic dysfunction and the development of the diabetic state.

Experimental support of our findings in the human being has just been published by Gaebler and Ciszewski,⁴ who demonstrated that in experimental diabetes in dogs, the diabetic state was markedly worsened and the insulin requirement was greatly increased by deprivation of the B complex. Addition of B complex to the diet

restored the former carbohydrate equilibrium.

Our clinical observations, as well as the experimental investigations mentioned, suggest strongly that nutritional deficiency is of etiologic significance in diabetes. From the standpoint of practical therapy, this concept has proved extremely valuable.

Lesions of nutritional deficiency occurring in diabetics are illustrated in koda-chrome.

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The Effect of Bed Rest and Immobilization upon Physiological and Chemical Functions in Normal Men

JOHN DEITRICK and DONALD WHEDON*†

Two healthy young men were studied during an eight weeks control period while on a regular exercise routine. They were then put to bed for six weeks in a bivalved cast reaching from the feet to the umbilicus. Following this period, observations were made during a four weeks recovery period. Diets were held constant throughout the entire experiment.

SUMMARY

1 A definite increase in nitrogen, calcium and phosphorus excretion occurred on bed rest. Sulfur and potassium excretion increased slightly. The maximum calcium excretion follows the maximum nitrogen excretion by approximately two weeks.

2 No correlation could be established between nitrogen excretion and 17-ketosteroid excretion.

3 In spite of increased calcium output there were no corresponding changes in pH and citric acid excretion which would increase the solubility of calcium.

4 Although there was immobilization of approximately half the body musculature no change in creatine excretion occurred. The creatine tolerance however did diminish on bed rest.

5 The most striking changes in functional studies were the loss of strength and the progressive failure of the circulation in response to the upright position.

* From the New York Hospital and Cornell University Medical College Department of Medicine, and the Russell Sage Metabolism Ward.

† This work was undertaken through contract with O.S.R.D. under the direction of the Committee on Convalescence and Rehabilitation of the N.R.C.

SURGICAL DIVISION
J WILLIAM HINTON, *Chairman*

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*The Rationale of Sodium Salts in the Treatment of Shock**

CHARLES L FOX, JR

Department of Bacteriology, College of Physicians and Surgeons, Columbia University

Recent studies by Richards support the view of Cannon and Wiggers that "reduction in the volume of blood returned to the heart is the keystone of all modern conceptions of shock." To discover the mechanism of shock it is then necessary to ascertain the cause of the "reduction in the volume of blood returned to the heart." The commonly accepted hypothesis is that of Blalock that "the decrease in blood volume could be entirely accounted for by the amount of blood or plasma lost at the site of local injury."

Since Blalock's studies in 1930, Gamble, Peters, Hastings and their associates have made important contributions regarding the chemical composition and distribution of body fluids. It was then found by Darrow and Yannet in animals, by Loeb, Harrop and Swingle in Addison's disease and by McCance after experimental salt deficiency in man that *external* loss of body sodium *without loss of plasma* resulted in reduction of blood volume, hemoconcentration, decrease in circulating plasma proteins, circulatory failure and typical "shock."

In shock following experimental burns, trauma, or hemorrhage, Rosenthal then demonstrated¹ the therapeutic efficacy of large volumes of isotonic solutions of sodium salts, "that the curative effects of serum are due to its electrolyte content", that concentrated albumin is without effect.

Clinical trial in 112 patients with burns² and 80 patients with shock from trauma and hemorrhage³ showed the benefit of oral and intravenous administration of volumes of isotonic solutions of sodium salts equal to 10 to 15 per cent of body weight. It is encouraging to note that the latest recommendations of the Shock Committee of the National Research Council advise a total volume of 8 to 15 liters of fluid (including

some blood or plasma) in the first 24 to 48 hours after injury.

The rationale for the sodium therapy of shock is explained by quantitative analysis of the chemical changes in tissues following severe trauma. These data were obtained by analyses with radiosodium,⁴ radiopotassium, and direct analytical methods totaling 2500 determinations. The results may be summarized as follows:

1 Large amounts of sodium and water accumulate in injured tissues, the gain in sodium exceeds the gain in water.

2 The potassium content of injured tissues is reduced, the decrease in potassium approximating the "excess" of sodium. This indicates breakdown of cell barriers with an exchange of extracellular sodium for intracellular potassium.

3 The protein content of injured tissues is *not* increased above that of contralateral uninjured tissues. Protein found in the edema fluid apparently is derived from the damaged cells rather than from the plasma as is generally believed.

4 Uninjured tissues of the animal in shock lose sodium but gain potassium, their water content remains unchanged. This indicates intracellular edema with extracellular dehydration. The increased hematocrit in shock also results in large part from swelling of the red cells.

5 The therapeutic indication is to restore blood volume by replacement of the sodium and water of the extracellular fluid and plasma diverted and removed by these tissue changes.

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* This work was done under a contract between the Office of Scientific Research and Development and aided by a grant from the Warner Institute of Therapeutic Research.

Improved Technique for Preparing a Buried Dermal Graft in Hernial Repair*

JAMES V SCOLA, 1st Lt, MC, AUS

This technique first is to denude the skin of the epidermal layer. Then the derma is cut away, making the graft of any desired size. This derma has subcutaneous fat attached to it, or if this is removed, the fibrous tissue at the base of the skin is attached to the graft. This subcutaneous fat or fibrous tissue on the undersurface of the skin offers a poor surface for a successful "take." The opposite side of the skin, however, (where the epidermal layer was removed) is an excellent surface for a successful "take." If the graft could be prepared so that both sides can take equally well, the chances of its viability are immediately doubled. It is the purpose of this paper to describe such a method.

Preoperatively, the thickness of the skin where the dermal graft is to be taken is roughly determined by gently pinching the skin. This is not difficult to do after trying it a few times. The peritoneum of the hernia is closed as usual and the fascial defect is measured. A dermal graft somewhat larger than the defect should be used.

Now the Padgett dermatome is set to cut a graft just short of the full thickness of the skin, thus leaving a very thin layer of epithelial cells on the donor site. This cut is usually between .04 to .05 inches, thus insuring a good thick graft. This graft is left attached at one end (A) as shown, cutting from (B) to (A).

The dermatome is now removed and reset to cut a very thin graft to remove the epidermal layer. This cut need not be over .008 inches (if the shellac used for the dermatome is made quite thin) and is made by

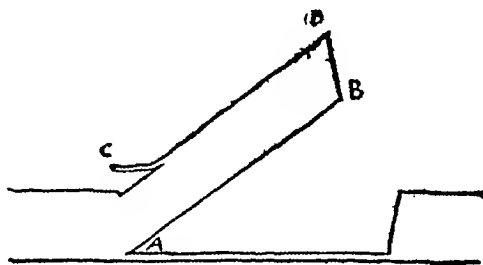


FIG 1 This figure represents the full thickness of skin. Subcutaneous tissue is not shown. The first cut with the dermatome is from B to A, thus raising the almost full thickness skin flap as shown. The dermatome is now removed, set to cut a thin layer of skin (not over .008) and the cut is made from C to B as shown. The graft is now removed by cutting across at A.

cutting from C to D. Allis forceps are used to spread the graft until it is stuck to the drum of the dermatome. When the dermatome is used for the second cut, the old shellac must be removed from the drum and new shellac applied to the drum and skin. The old shellac need not be removed from the skin.

The dermal graft is now removed by cutting it across at A. The graft is sutured to good fascia surrounding the defect, using interrupted silk sutures. A very light sprinkling of sulfanilamide powder may be applied over the graft if desired. The subcutaneous tissues are approximated over the graft, obliterating all dead spaces. The site where the graft was taken is covered with vaseline gauze and left undisturbed for seven to ten days.

A series of five cases is reported in four of which there was either no fascia to approximate or the fascia was too thin and frayed to be used for repairing.

* From the Graduate School in Surgery, New York Medical College and Flower Fifth Ave. Hospital. Presented by Joseph H. Fobes, Head of Graduate Surgery.

Therapeutic Effect of Radioactive Iodine on Adenocarcinoma of the Thyroid with Functioning Metastases

S M SEIDLIN and L D MARINELLI

This is a report on a patient, 52 years old, who had a complete thyroidectomy for a "malignant adenoma" in 1923. He had no thyrotoxicosis then nor hypothyroidism post-operatively. Fifteen years later, he developed classical symptoms of hyperthyroidism (B M R + 40%) and severe pain in the lower back. In October, 1939, a pulsating tumor was removed from the level of the thoracic 12th and proved to be metastatic thyroid carcinoma (histologically, small follicles, well-differentiated with colloid). In the next two years, hyperthyroidism increased and x-rays revealed metastases in the lungs, right upper femur, second left rib, pelvis, and skull.

Deep roentgen therapy was ineffective.

Lugol's solution therapy showed slight but definite effect on the hyperthyroidism. Geiger counter-studies after the administration of a tracer dose of radio-iodine demonstrated uptake by *all* the lesions. Thiouracil administration produced a typical remission of the hyperthyroidism, which recurred after cessation of treatment. Several massive doses of radio-iodine resulted in a striking improvement of the clinical picture. B M R dropped to below normal, patient gained weight and there was a complete arrest in the growth of the metastases. Quantitative studies on the pick-up and excretion of the radio-iodine by the metastases were carried out. Thyrotropic hormone studies were also made.

* * *

*Pulmonary Suck and Blow as a Respiratory Analeptic, Interdependence of Cardiac Massage and Suck-and-Blow Resuscitation**

* From the Graduate School in Surgery, New York Medical College and Flower Fifth Ave. Hospital. Presented by Joseph H. Fobes, Head of Graduate Surgery.

JACOB REICHER

Based on Thompson and Birnbaum's demonstration of the "phenomenon of asphyxial resuscitation" by pulmonary suction and deflation (suck-and-blow), evidence is presented that combined suck-and-blow with cardiac massage serves as an effective resuscitant where either alone fails. Additional experiments are presented indicating that such a combination would be inadequate if the pulmonary ventilation consisted of either pressure alone or suction alone. It is emphasized that the application of suck-and-blow to the pulmonary tree does more than create an interchange of gases; the procedure serves as a true analeptic

since it actually *stimulates* respirations mediated through nervous mechanisms. External methods of artificial respiration (manual, Drinker, Bragg-Paul, etc.) merely serve as substitutes for respiration; they do not stimulate.

A summary of the physiology of respiration is presented as it applies to suck-and-blow, and a résumé is made of the history of suck-and-blow devices. Asphyxia is discussed, as well as the arguments pro and con in the various methods of resuscitation including chemical analeptics in contradistinction to the reflex analeptic, pulmonary suck-and-blow.

*The Reaction of the Peripheral Circulation to Cold in Scleroderma, Raynaud's Disease and Thrombo-Angitis Obliterans**

H R MILLER, J MARRUS, M S and BEVERLY C SMITH

On the basis of results in acclimatization carried out on normal subjects in the Climatic Research Unit of the Signal Corps, Fort Monmouth, investigations were undertaken to determine the reaction of the circulation of the extremities exposed to intense cold in subjects with scleroderma, Raynaud's disease and TAO

Cold normal digits revealed an ability to warm up spontaneously (phasic rise and fall in skin temperature) Warming could also be induced by temporarily occluding the circulation of the limb or by having the subject breathe CO₂ enriched mixtures

The cold digits in the pathological conditions exhibited two types of reactions (1)

spontaneous warming, i.e., phasic rise and fall in digital skin temperature as in normal subjects, (2) a progressive rise in digital skin temperature which lasted several hours The latter reaction especially was associated with increased tolerance to cold, diminution in pain, subjective sensations of warmth and comfort in the parts exposed to severe cold, and with signs of clinical improvement in some cases

The investigations have demonstrated that in scleroderma, Raynaud's disease and TAO, it is possible to induce a marked and sustained increase in digital skin temperature. This response may have therapeutic value

* From Columbia University College of Physicians and Surgeons

* * *

The Functional Pathology of Experimental Frostbite and the Prevention of Subsequent Gangrene

KURT LANGE and LINN J BOYD

The tissue alterations after exposure to severe cold were described and the sequence of events was illustrated by pathologic slides as well as kodachromes of fluorescein tests performed at different intervals after exposure.

Cold sufficient to solidify the exposed tissues causes a complete interruption of circulation during exposure This is always followed by a period of complete restoration of circulation and increased capillary permeability as evidenced by the fluorescein test. This period lasts for 6 to 16 hours after exposure This is the most promising period for therapeutic endeavors The period of circulatory restoration is followed by one with arteriolar and capillary occlusion resulting from the formation of red cell clots Gangrene of the associated area

is the consequence.

Heparin administered during the period of circulatory restoration prevented gangrene in 16 rabbits whereas all controls had complete gangrene of the part. Five animals were exposed by freezing small areas In the remaining animals the entire hind leg was frozen

Although tissue loss was completely prevented by the early use of heparin, sensory and motor nerve paralysis was often not prevented

A case of severe human exposure in which loss of tissue was to be expected was treated with heparin and gangrene was completely and successfully prevented

Later experiments in human volunteers also showed the validity of this treatment in cases of human frostbite

Heparin in the Treatment of Experimental Human Frost Bite

LEO LOEWE, KURT LANGE and PHILIP ROSENBLATT

The functional pathology of experimental frost bite in the rabbit has been elucidated by Lange and Boyd¹ through the medium of the fluorescein test. In the initial stages of frost bite there is merely clumping of erythrocytes in the small vessels due probably to loss of plasma through the highly permeable vascular walls. These stranded red cells which silt up the blood vessels forming a sludge do not, in the beginning, represent true thrombi. Organization into thrombi supervenes only after approximately 72 hours. They discovered that thrombosis and complicating infarctive gangrene after experimental frost bite could be prevented by heparinization, if started early.

Experiments were projected in human volunteers to (1) reaffirm the effectiveness of early heparinization, and (2) to develop

a simple practical therapeutic program. For the latter, subcutaneous heparin/Pitkin Menstruum was the method of choice.

Experimental frost bite was induced in human subjects by applying to the skin the bottom of small porcelain crucibles filled with dry ice. The controls developed necrosis of the exposed area, while the adequately heparinized subjects, apart from superficial blistering of varying degree, escaped any deeper injury. Further experiments are in progress.

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* * *

Repository Injection of Penicillin in Water-in-Oil Emulsion Effect on Gonorrhea

A COHN, B. A. KORNBLITH, I. GRUNSTEIN, K. J. THOMSON and
JULES FREUND

A study was undertaken to determine if penicillin injected intramuscularly is more effective in a water-in-oil emulsion than in aqueous solution. It was hoped that the absorption of penicillin might be prolonged by incorporating it in a water-in-oil emulsion so that the number of injections and perhaps the amount of penicillin could be reduced.

Single doses of water-in-oil emulsions of penicillin were prepared by a simple rapid-technique as follows. One and four tenths

cc of sterile 0.85 per cent salt solution are drawn into a sterile syringe and ejected into a vial containing 100,000 O. U. of dry penicillin. To the penicillin solution 31 cc of an autoclaved mixture containing 11 parts of a lanolin-like substance (Falba) and 20 parts of peanut oil are added by means of a sterile syringe and a 17 gauge needle. With the needle still inserted through the rubber cap of the vial the mixture can be readily emulsified by repeated withdrawals and rapid reinjections.

into the vial. As soon as the mixture assumes a uniformly creamy, slightly viscid consistency, satisfactory emulsification has occurred. The mixture is then ready for intramuscular injection.

Serum penicillin concentrations in patients with gonococcal infections after a single intramuscular injection of 150,000 O U of penicillin yielded detectable amounts of penicillin in a range of 2.5 O U per cc. within half an hour after injection to 0.008 O U per cc. 7 hours after injection. Corresponding determinations of urinary excretion of penicillin yielded ap-

preciable amounts of penicillin as long as 28 hours after the original single injection.

The results of treating 52 patients with gonococcal infections by a single repository injection of 150,000 O U of penicillin were 50 cures and 2 failures. Forty-nine additional cases were treated by a single injection of 100,000 O U of penicillin in water-in-oil emulsion to which was added a "priming" dose of 50,000 O U of penicillin in aqueous solution simultaneously. No failure was observed in this group. No toxic side effects were observed, the local site of injection showed no untoward reactions.

* * *

*The Oral Administration of Penicillin in Normal Subjects and in Patients with Pneumococcus Pneumonia**

WALSH McDERMOTT, PAUL A. BUNN, MARIA BENOIT,
REBECKAH DU BOIS and WILLETTA HAYNES

Department of Medicine, Cornell University Medical College and New York Hospital

The oral administration of penicillin by a number of methods, which have included the use of oil, oil and beeswax, aqueous solution preceded by a buffer, and aqueous solution alone, has been investigated in a series of normal subjects and patients with pneumococcus pneumonia. It was concluded that

1. It is possible to attain blood penicillin concentrations after administration comparable to those attained after intramuscular administration by the use of approximately five times as much penicillin.

2. As the concentrations attained in the blood, and the amount excreted in the urine following the ingestion of penicillin in four

different vehicles including water were all of the same order of magnitude, it would seem that none of the vehicles studied protected the penicillin from destruction in the body and that the absorption which occurred was merely a reflection of the amount of penicillin which was ingested.

3. The therapeutic results attained following orally administered penicillin to forty patients with pneumococcus pneumonia were comparable to those observed after intramuscular therapy and were equally satisfactory whether the penicillin was administered in oil, in water, or as the dry powder in a capsule.

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University.

Subclinical Trichinosis A Clinical and Pathologic Study

S E GOULD

Eloise Hospital

A surprisingly high incidence of trichinosis infection (as high as 29.3 per cent, according to the method of examination used) was found in persons coming to autopsy at Eloise Hospital, the county hospital of the Detroit area. A study was undertaken to determine the value of intradermal and precipitin tests and eosinophilic cell counts in the diagnosis of old subclinical trichinosis. The results of these tests made during life were correlated with the presence or absence of *Trichinella spiralis* in those persons who had been clinically tested and who later came to autopsy.

Of 3501 patients who had been skin-tested with trichina antigens, 388 were examined for trichinellae at autopsy, of 548 who had had blood precipitin tests, 66 came to autopsy and were examined for larvae, while 886 patients who had had eosinophilic cell counts during life were similarly investigated for trichinae post mortem. It was found that the trichina

intradermal and precipitin tests and the eosinophilic cell count cannot be relied upon to indicate the presence of old subclinical trichinosis. Eosinophilia usually persists 6 months and rarely more than a year after infection. It is believed that the blood precipitin test remains positive for 1 or 2 years and that the immediate type of intradermal reaction may be elicited, on the average, for nearly 10 years after infection. The immediate intradermal test was found to be more sensitive and easier to read than the delayed intradermal test. About 5 per cent of reactions obtained with the immediate intradermal tests were non-specific in nature and were believed to be possibly due to sensitization induced by antigenic material in non-viable trichinae present in ingested pork. The possibility of obtaining either non-specific intradermal reactions, or specific reactions from previous trichinosis infection, should be remembered in testing patients with suspected clinical trichinosis.

* * *

Methods for Achieving Optimum Penicillin Blood Levels Including the Use of Enhancing Agents Such as Para-Aminohippuric Acid

LEO LOEWE, PHILIP ROSENBLATT and ERNA ALTURE-WERBER, Ph D

This study was undertaken to determine optimum penicillin dosages in patients with subacute bacterial endocarditis who were refractory to treatment, and also, those infected with *Streptococcus sbe*. In view of ineffective penicillin blood levels obtained with standard dosages in these resistant patients, it was necessary to employ huge amounts of penicillin before achieving therapeutic levels. Because of the non-toxic character of the presently available penicillin, dosages up to thirty million Oxford units per day were administered by continuous venoclysis. The uninterrupted flow of this massive dosage, which was well tolerated,

was made possible only by the conjoint use of heparin. Continuous intramuscular administration could not be employed because of the severe pain, local reaction and fever induced. Blood levels of 60 Oxford units per cc were obtained. To conserve penicillin, enhancing agents such as para-aminohippuric acid were successfully employed in some experiments. The clinical importance of these results is evident in connection with resistant organisms in subacute bacterial endocarditis and also in the management of the group of diseases caused presumably by penicillin insensitive types of organisms.

Sudden Deaths in Infancy

JACOB WERNE and IRENE GARROW

The investigation of sudden deaths during infancy has, in the past, been relatively unsatisfactory. These cases have usually been certified as due to accidental mechanical suffocation if the subject has been found dead in the crib, or as status thymico-lymphaticus if the death occurred under other circumstances and still remained unexplained at autopsy.

The authors have been studying this problem for the past 14 years in the Office of The Chief Medical Examiner, Borough of

Queens, and conclude that the sudden death of an infant, unexplained by gross findings at the autopsy table, will, on further investigation (microscopic, bacteriologic and epidemiologic), prove to be an expression of fulminating infection, usually respiratory in origin.

This presentation summarizes the completed study of some 200 cases, including control material consisting of infants dying of trauma and of those dying of known respiratory infections.

* * *

An Investigation of Type Specific Meningococcic Agglutinins in Human Serum. II—Immunological Response of Proved Cases of Meningococcic Infection

CAROLYN R. FALK and EMANUEL APPELBAUM

Bureau of Laboratories of the Department of Health of the City of New York

The meningococcus agglutinin content of 252 bacteriologically proved cases of meningococcic infection was studied over a three-year period during which the incidence of this disease was high. Samples of serum were taken from the same patient from 1 to 84 times at intervals of from 1 to 21 days, and were representative of the acute, subacute, and convalescent stages.

Agglutinins in significant titers were found in 46 per cent of serums obtained during the acute, in 79 per cent of serums taken during the subacute, and in 68 per cent of serums obtained during the convalescent phase. The agglutinins appeared most regularly at the end of the first week of illness and reached a maximum titer during the second and third week. There was considerable individual variation as to the length of time that agglutinins persisted. The titers fell to pre-infection levels between the third week and the fourth month after onset.

Agglutinins for Group I, Group II, and Group II-alpha meningococci were found alone or in combination with each other. The agglutinins corresponded in prevalence with the type distribution of the infecting organisms. The type of the agglutinins found in the patients' serums corresponded with the homologous infecting organism in the 82 cases where both the infecting organism and the serum were available for study.

The agglutination test may be useful in determining the type of the infecting organism in cases where meningococci were not cultured from the blood or spinal fluid and in which the "Quellung" test was unsuccessful. This test may also be of value as an additional diagnostic procedure in cases of suspected meningococcic infection where other laboratory confirmation is lacking. In this connection the importance of performing several tests to demonstrate the change of agglutinin titer cannot be over-emphasized.

Morphological Studies of Salmonella Typhi Murium and Salmonella Enteritidis in Guinea Pigs and Mice

ALFRED ANGRIST and MOLLIE MOLLOV, B S, M A

Above strains of salmonella organisms, recovered from human cases coming to autopsy, were fed to guinea pigs and mice, to note the morphological changes, particularly in the early stages. The source of the typhi murium organism was a case which came to autopsy with a typical picture of typhoid fever histologically.

One cc. of an 18-hour broth culture was fed to guinea pigs weighing between 250 and 300 grams, and $\frac{1}{4}$ cc was given to 18-to-20-gram mice. Natural infection was ruled out before the feeding experiments. Infected animals were killed at varying periods, or when they appeared ill. Post mortem cultures and sections for histological study were taken of the heart, liver, spleen, nodes and intestine of the infected animals, as well as from the control group. In all cases, the original organisms were isolated from the infected group only.

The detailed morphological studies of the

reaction in the Peyer's patch are presented. The exudative and proliferative changes, and the necroses selectively localized to such delimited areas of the gut (Peyer's patch) permit of the study of the early phases of bacterial invasion. The theoretical implications of the above morphological observations as to the mechanism of infection and of the necroses with sloughing and ulceration, as they apply to human paratyphoid and typhoid infections, are discussed briefly.

The reaction in Peyer's patches and the regional mesenteric lymph node tissue seems to be independent of the antigenic structure and to be contingent upon the relative general virulence of the organism and the resistance of the host, portal of entry and method of insertion in this instance. A parallelism with primary tuberculosis is drawn.

* * *

Oral Administration of Penicillin for Treatment of Gonococcal Infections

ALFRED COHN, BORRIS A. KORNBLITH and ISAAK GRUNSTEIN

Experimental observations of Schnitzer and Ercoli showed that mice infected with various organisms responded to oral therapy with penicillin.

They also found that when humans were given single doses of 120,000 O U of penicillin by mouth the blood serum levels varied between 0.05 and 0.4 per cc. within 1 hour and dropped to less than 0.001 within a period of 2 to 8 hours. When 240,000 O U were given, blood serum levels ranged between 0.1 and 0.4 O U within 1 hour and gradually dropped to 0.025 O U per cc. within a period of 3 to 5 hours. Two subjects receiving 120,000 O U and 240,000 O U respectively failed to show any ap-

preciable blood serum penicillin level.

In view of these findings 40 patients with gonococcal infections were given oral penicillin therapy in tablet form. In a group of eleven patients 800,000 O U of penicillin were given in divided doses of 60,000 O U every 2 hours over a period of 8 hours. Another group of 29 patients received 600,000 O U in divided doses of 120,000 O U every 2 hours over a period of 8 hours.

Of the total of 40 patients treated, 30 were cured and 10 failed to respond to this form of therapy. The percentage of failures in each group was practically the same. No toxic side effects were observed.

*Experimental Study on the Activity of Penicillin Administered Orally in
Experimental Streptococcus, Pneumococcus, and Meningococcus
Infection of Mice*

R J SCHNITZER, N ERCOLI, D J LONGACRE and G Soo-Hoo, M S

In large series of experiments, it was shown that sodium penicillin administered orally in aqueous solution exerts a striking therapeutic effect in all experimental infections which respond to the parenteral administration of penicillin. A comparison of the dosage required to protect at least 60 per cent of the intraabdominally infected animals showed that the ratio

minimal oral dose
minimal subcutaneous dose

varies with the

different infections

In infections with the very sensitive β -hemolytic streptococci and with pneumococci type 1 and type 2, this ratio was 10, indicating that a 10 times higher dose of penicillin was required by the oral route. Infections with *Staphylococcus aureus* and meningococci required higher doses for the subcutaneous treatment, and in these cases,

the ratio oral/subcutaneous-treatment became much smaller and was found to be not more than 2.5 for the staphylococcal and 1.0 in the meningococcal infection.

We found these observations confirmed in 3 more experimental infections which also could only be controlled by comparatively high doses (2000-4000 units) of parenterally administered penicillin. In infections of mice with *Salmonella schottmülleri*, with *Borrelia novyi*, and in the intranasal infection of mice with type 2 pneumococci, the ratio was 1.0 to 2.0.

Although the determination of the penicillin concentration in the serum allowed an interpretation of these findings to a certain extent, the effectiveness of penicillin treatment seemed to depend largely on the susceptibility of the infecting microorganism and on the defense mechanism of the host.

* * *

The Proteolytic Activity of Serum and Plasma

L R CHRISTENSEN, Ph D and COLIN M MACLEOD

The presence of proteolytic activity in serum and plasma has been known for many years. In general the activity is not demonstrable unless the serum has first been treated with chemical agents, such as chloroform and other organic solvents, organic compounds, such as urea and cresols, or unless the serum has been treated by dialysis or acidification. Recently it has been shown that the phenomenon of streptococcal fibrinolysis is due to the activation of a serum enzyme by streptococcal fibrinolysin.

Evidence will be presented indicating that the enzyme activated by fibrinolysin and that activated by other agents are identical. Characterization of this enzyme in regard to the effects of pH and temperature on its activity, and to the effect of certain specific protease inhibitors indicate that the enzyme differs from known enzymes and

probably represents a specific protease, characteristic of serum. Data will be presented indicating that activation of the enzyme by streptococcal fibrinolysin is an enzymatic type of reaction, suggesting the conversion of the inactive enzyme or zymogen in serum to an active state by streptococcal fibrinolysin, a kinase, analogous to the enterokinase activation of trypsinogen.

A nomenclature is suggested for this serum enzyme system analogous to that used for other proteases. The active enzyme is termed "plasmin" to denote its origin, the plasma. The enzyme, as normally present in the blood, is termed "plasminogen" to denote its inactive or zymogen state. Fibrinolysin is termed "streptokinase" to denote its origin and action.

Certain implications of these findings will be discussed.

*The Use of Radioactive Sodium in Studies of Circulation in the Extremities**

BEVERLY C SMITH and EDITH H QUIMBY, Sc D

With the continually lengthening span of life, more persons live to develop degenerative arterial disease in the extremities. Pathological arterial changes alter circulation time, volume of blood circulating in the extremity, and relationship of plasma and extravascular fluid. Any means of obtaining information regarding these matters should be helpful in diagnosis and prognosis. We here report a method whereby intravenous injections of small amounts of radioactive sodium are used in circulation studies.

The radioactive sodium is obtained from the cyclotron laboratory of Columbia University, it is prepared in sterile saline for intravenous use. The disintegrating radioactive atoms are detected by a Geiger-Muller counting apparatus which gives an audible click for each disintegration.

The test is carried out as follows. The patient lies on his back, and the shield containing the Geiger-Muller counting tube is placed against the plantar metatarsal region of the foot. The desired amount of radiosodium is injected into an ante-cubital vein. The electric stop-clock and the injection being started simultaneously, the clicking of the counter indicates the arrival of the material at the foot, and the arm-to-foot circulation time is immediately established.

If the counter is kept in position against the foot, and counts are made each minute, the counting rate is found to increase steadily, quite rapidly at first and then

more slowly. This is due to the interchange of sodium between plasma and extravascular fluid until equilibrium is reached between the two. The pattern of the build-up curve depends on the blood supply, the state of the vessels, and other conditions in the extremity. Circulation time and build-up pattern for normals have been established, and similar studies have been made in some 200 diseased individuals. These include fairly extensive series of patients with hypertension, arteriosclerosis, diabetes and thromboangitis obliterans, and smaller groups with a wide variety of conditions.

When the main peripheral and collateral vessels are normal, the build-up pattern is that of the normal individual. If the main peripheral vessels are not palpable and oscilometric readings are absent or low, the rate of build-up largely measures the existing collateral circulation, and the nearer this approaches to the normal pattern the more adequately is the collateral circulation able to carry on the function of the impoverished main vessels.

These observations have been found to parallel closely clinical history and observation. They are now being used as a guide to therapy. In particular, a demonstration of adequacy of circulation in a projected amputation site has been of considerable aid in conservative surgery. Repetition of the test at intervals during or following therapy affords an estimate of the patient's progress.

* From the Departments of Surgery and Radiology, College of Physicians and Surgeons, Columbia University, with the aid of a grant from the Lilla Babbitt Hyde Foundation.

BULLETIN OF THE NEW YORK
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
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SEPTEMBER 1945

THE PHYSICIAN AND THE PROBLEM
OF ALCOHOLISM *

HOWARD W HAGGARD

WHAT I shall have to say this afternoon on alcoholism is directed not at all to the specialist treating this disease but to the non-specialist, the physician who meets the alcoholic and his family as incidental to his practice of medicine. The practitioner cannot usually be expected to treat the alcohol habit competently, nor would he, as a rule, wish to attempt this treatment. But nevertheless the part he plays toward the success or failure of eventual recovery of the alcoholic is often the crucial part. It is to the physician that the problems of the alcoholic and his family are usually brought first. It is the attitude of the physician which, in great measure, determines the course which the alcoholic will follow and also the understanding and cooperation—or lack of them—which the alcoholic and his family will show. A great many former alcoholics, who today occupy important and respected positions in our society, owe their eventual rehabilitation to the competent primary guidance of their physicians. There are, I am sorry to say, many, probably a great many more alcoholics who did not receive good primary guidance and for whom their physicians were not aids but actual, and sometimes insurmountable, obstacles to recovery. We

* Friday Afternoon Lecture at The New York Academy of Medicine, January 26 1945

usually think of that basic Hippocratic aphorism of our profession, *prima non nocere*—first do no harm—as applying only to misuse of drug and knife, but in respect to alcoholism the misuse of word and attitude may be equally harmful

I shall devote much of my talk to this matter of the attitude of the physician toward the alcoholic and the influence of this attitude upon the treatment for alcoholism. But first, I want to try to clarify a common misunderstanding which has frequently influenced the scientific if not the personal attitude of the physician toward the alcoholic and his problem. It is the misconception of alcoholic as contrasted to alcoholism, one concerns the man and the other his habit. I have said that the non-specialist practitioner cannot usually be expected to treat alcoholism, he can, however, most competently treat the alcoholic. This is not a quibble in terminology, there is a vast difference between the two which is frequently overlooked. The treatment of the alcoholic consists in sobering up the man, giving him some symptomatic relief, determining and remedying his physical disturbances, correcting his dietary deficiencies, keeping him under good medical and hygienic care until some measure of normal physical health is restored. Unfortunately, some physicians, and even some institutions, consider this an ultimate treatment. Under their care the alcoholic, in a week or a month, may show marked physical improvement, he may even stop drinking for another week or another month but in the great majority of instances he starts his heavy drinking again. This relapse and a second, a third, a fourth and a fifth, each following a period of treatment of the alcoholic, are discouraging. It leads to pessimism not only as to the expectation of more than temporary benefits of physical rehabilitation but also, and more important, as to the probability of any recovery from alcoholism. The pessimism shows in the attitude of the physician toward the alcoholic, it is sensed acutely by him to the detriment of any subsequent therapeutic success.

Actually the pessimism is not justified. It is not surprising or discouraging that a habit persists when treatment is not directed to the habit but only to the physical derangements which are results and not causes of the habit.

Again, the pessimism of the physician may originate in or be reinforced by two undeniable facts which seem discouraging in their bald statement but which are far from discouraging in their interpreta-

tion The first is that alcoholism cannot be cured That, today, in the great majority of instances, is scientifically correct But it is correct only if the physician will insist upon the same rigid definition and use of the word "cure" when applied to other diseases There is no specific for alcoholism as there is for syphilis Likewise, there is none for tuberculosis and typhoid fever, but this lack does not impart a corresponding pessimism as to a possible recovery The fact that there is no cure, in the strictest sense of the word, for these diseases does not deter the physician from applying every measure which will give the greatest opportunity for recovery We are prone to forget that the tremendous advancement of medicine which arouses our enthusiasm has by no means taken all of the truth from the modest words—now 400 years old—of Paré "I treated him, God healed him" Or perhaps you might prefer to say it impersonally, but with equal medical humility and understanding "He got well under treatment"

The second undeniable fact is that recovery from alcoholism nearly always means only that the former alcoholic has ceased to drink and, of course, has become rehabilitated It rarely means that he has regained or obtained what might be called a normal reaction to the use of alcohol The compulsion to drink excessively is not eradicated, it is simply brought under control and it is held under control but only as long as no alcohol is taken One drink, and the compulsion may again dominate Recovery from the habit is usually a symptomatic recovery only

These two facts must be recognized and they must be faced not only by the patient but also by his physician They are not discouraging facts that can be construed to give to the physician—and through him to the patient—the obstacle of disbelief in recovery The important fact is that with proper guidance a high percentage of alcoholics can learn to control their habit and become rehabilitated And most of them are—even aside from any humanitarian consideration—well worth rehabilitating

There are many forms of treatment for alcoholism and, for all, recoveries are claimed and no doubt obtained Multitherapy always arouses suspicion in the mind of the physician, for from experience he knows that any malady which has many treatments has no good one But the assumption that because there are many treatments with recoveries from alcoholism, none is valid must rest upon a *a priori* assumption that the excessive use of alcohol, the determining symptom,

has always a common etiology I do not think that it can be shown that there is a common etiology for excessive drinking

Such a statement implies disbelief in physical, chemical, or pharmacological idiosyncrasy as the basis upon which excessive drinking rests. The discovery of such a basis, if one could ever be made, would hold out great promise not only for the pharmacological cure of alcoholism but also for the more important prevention by the designation, from tests, of those who were susceptible to alcoholism and therefore must never drink. The psychiatrist, from his inability to find a definite prealcoholic type of personality, is prone at times to pass the matter back to the physiologist and pharmacologist. It is true that he raises pertinent questions, such as these: Some men with manic depressive psychosis drink to excess, especially periodically, but others with this psychosis do not. Why, when alcohol is universally available and widely experienced, do some find a partial symptomatic relief in drinking and others do not? The same applies to the early schizophrenic. Some become violent symptomatic drinkers, others do not drink at all. Among alcoholics there appears to be a large number of psychoneurotics, but there is a vastly larger number of psychoneurotics of equal or even greater involvement who, with like opportunity, do not drink to excess. Such facts as these quite naturally suggest the possibility of a somatic common denominator acting among those who turn to alcohol. None which is valid has ever been found, and in the extensive physiological studies dealing with the action of alcohol none has ever been soundly indicated.

One especial feature characterizing the drinking behavior of many alcoholics has led some authors to the postulation of an allergic-like reaction to alcohol which, by them, is taken as a common denominating somatic factor. This so-called allergy has as its major manifestation not the usual allergic reactions, but instead, uncontrollable drinking after a drink is taken. That is, the alcoholic can become abstinent and can remain so but he cannot become moderate in his use of alcohol. His action is none, or all.

The conception of an allergic-like response to alcohol has had a measure of recent popularity because it is particularly acceptable to the alcoholic. First, in view of the wide popular interest in allergies for foods and pollens, the alcoholic can find an understandable explanation of why he must shun all alcohol, second, the allergy idea pro-

vides the alcoholic with an excuse which receives sympathetic understanding when he refuses a drink with the explanation that he is "allergic" to alcohol, and third, he is given an ego satisfaction, which he needs badly, in being physically rather than mentally or morally different from the majority of human beings and in having no volitional responsibility for this difference. The acute sufferer from asthma, hives and hay fever rarely appreciates the distinction conferred by his allergy, but the individual who, after taking one drink, invariably goes on a spree may find considerable comfort in the explanation that his behavior is due to an unfortunate body chemistry.

Now, as a matter of fact, when the literature is searched carefully to follow the rise of the concept of an allergic origin of craving it is found that with few exceptions the idea advanced has been mainly metaphorical. The actual term used has been "psychic allergy" or a "psychobiological sensitivity which is practically an allergy" which perhaps may be defined as a condition of exaggerated response in which the allergen is a mental or emotional state. It is doubtful if the readers of such statements—and certainly not the patient to whom they are repeated—note the qualifying term of psychic, psychic allergy, which removes the matter from somatic cellular reactions and restores it to mental reactions. The more familiar ideas of chemical allergy to foods and pollens tend to blind one to the qualification of "psychic allergy" and lead to the inference of a true chemical allergy to alcohol for which there is no scientific basis.

The attempt to express alcoholism in terms of allergy is not surprising in light of the long history of the effort to find a pharmacological basis. Similar attempt has been made to attach the basis of alcoholism to many medical discoveries which have attracted wide popular interest. Thus, near the end of the last century attempts were made to prepare an immunizing serum from gradually alcoholized horses. Toxic states, gouty impurities, and endocrine disturbances have all been advanced as causes. Such attempts have not failed because they advanced a single etiology or a somatic etiology, but because they advanced false etiologies.

The lack of a defined common etiology means that the practitioner in dealing with his alcoholic patient, must make some differentiations if he is to direct his patient to the most advantageous therapy—the one best suited to the alcoholic. At this early stage there comes an im-

portant qualification, it is the one of economics. If the patient can afford possibly long and necessarily expensive care, the diagnosis and full responsibility for therapy and rehabilitation can be shifted to one of the competently staffed private institutions treating alcoholism (in contrast to those treating only the alcoholic as I developed earlier). In many, perhaps the majority of instances, the alcoholic cannot afford this care. The responsibility of obtaining the most advantageous therapy that the patient can afford then rests upon the physician. The selection of the therapy involves preliminary diagnostic study but of a sort that requires no extensive psychiatric sophistication. The questions before the physician are: First, is this patient an alcoholic? And second, if so, what general sort of alcoholic is he?

The first question enters only occasionally. Usually the history of the individual leaves little doubt that he is drinking in great excess but occasionally there is doubt. Once in a while an individual who is distinctly hypochondriacal will volunteer the statement that he fears alcohol is getting the better of him and that he is becoming an alcoholic. More often perhaps the wife or the mother comes to the practitioner with the statement—based often on a complete lack of sophistication or, more likely, on strong anti-alcohol convictions—that her husband or son is an alcoholic. Such statements are frequently expressions of a losing part in an argument on the question of any use of alcohol, in which reinforcement from the physician is sought.

The presumed alcoholic, brought or forced to the physician by a member of his family is, as a rule, not in a favorable situation for that rapport between the physician and patient which is necessary for the successful treatment of alcoholism. Somewhat more favorably situated is the patient who is under treatment for some somatic complaint and in whom the physician discovers the probability of alcoholism. Both such patients may stoutly deny that they are alcoholics. It would seem undesirable that the physician make his decision wholly on the basis of the amount of alcohol consumed per day unless that amount is so large as to be unmistakably excessive even under the most liberal standards. I have heard physicians discuss the matter of amounts of drinking that indicate alcoholism and these amounts vary only with the physician's personal convictions and habits and hopes. Thus I have heard physicians say that they considered as an alcoholic anyone who daily drank two glasses of beer or two ounces of whisky, and I have

heard others dismiss with a shrug the drinking of a pint or more of whisky a day, over a long period of time

Again, it may be well to remember that in stating amounts consumed daily, both the alcoholic and his family are often biased and consciously or unconsciously over- or under-estimate. One of the best tests for many, but not all, alcoholics is not in amount, not in asking the possible alcoholic to see if he can abstain entirely—for many can—but to limit his drinking for a time strictly to two drinks a day. That, most cannot do. And the fact that he cannot, may, for the first time, bring home to the patient the fact that he is actually an alcoholic and does not have the control over his habit which he believed he had.

Having established the fact, or presumption, that the patient is an alcoholic, the next diagnostic measure—barring the physical examination—would be to make an evaluation as to what sort of alcoholic the patient is. There are numerous and elaborate classifications but a convenient and sufficient, but quite arbitrary one, for the general purposes with which I deal is (1) symptomatic drinking, (2) true addiction, and (3) secondary addiction. The distinctions are, as I say, arbitrary and open to psychiatric argument which I certainly would not attempt to defend. But for the purposes here, I think it may be taken that the symptomatic drinker is a man whose excessive drinking is one of many possible symptoms of some deep-seated disturbance—possibly a psychosis. Some diagnostic guidance may be had from the nature of the drinking. If it is periodic, perhaps at intervals of several months, with abstemious periods, the possibility of a manic depressive psychosis in which the patient drinks in either the manic or depressive stage may suggest itself, likewise suggested may be epileptic states, and occasionally severe endocrine dysfunction. If symptomatic drinking is steady, wild and witless, the possibility of early schizophrenia (especially if the patient is young) or early general paresis, may be suggested. Recovery from alcoholism under any form of treatment directed only at the alcoholism is useless in the symptomatic drinker. Psychotherapy, aversion therapy, or counselling by Alcoholics Anonymous would lead only to failure with the possible reinforcement of the pessimistic idea that treatment for alcoholism is hopeless. Thorough psychiatric examination is indicated before any time is wasted in treating the habit of the symptomatic drinker.

In most classifications, a distinction is made between so-called true

addicts and secondary addicts. The distinction is mainly that of degree of psychopathology inherent in the drinker before he started drinking. The true addicts have a profound but non-psychotic maladjustment, they are the most dramatic and the most pitiful of the excessive drinkers but fortunately, at present, the smallest group. I put in the qualification of "at present," for a profound and widespread alteration of social and economic conditions may lower the level at which maladjustment of personality is manifest. The true addicts make up the group that occupies a prominent position in popular and medical views, because they express to the highest degree the general conception of the true alcoholics—the men to whom alcohol is a complete solution to the problem of adjustment. They do not respond well to treatment, but they are not entirely hopeless, for if they can be shown and convinced that their conflicts can be relieved by means other than alcohol, they may develop more acceptable behavior. They, again, are not the type of alcoholics for whom the aversion treatment or the counselling of the Alcoholics Anonymous, or any treatment on a similar plane, would be likely of success. They are the problems, and the difficult problems, for the psychotherapist in the broadest use of this term.

So far, I have tried to differentiate two broad classes—I might say exclude them—on the basis of maladjustment so severe that abolition only of the symptoms of excessive drinking and rehabilitation would yield an individual who was still unable to make adjustments even approaching the normal. After this exclusion, there is left a very large number of alcoholics whose prealcoholic psychopathology falls within that wide and indefinite range for individuals who could make reasonably normal adjustments. They were not, before their alcoholism developed, severe psychoneurotics, they are men whose drinking habits have become abnormal under the influence of predominantly exogenous factors—including alcohol itself.

No prealcoholic personality type has been differentiated for this large group of alcoholics to which I have reference here. Possibly searching psychiatric examination might indicate certain tendencies but as yet none has been found which is sufficient for the selection, with any certainty, of potential alcoholics of this group. After the alcoholism has become well developed, however, certain general personality or character traits seem to appear, to be superimposed or possibly uncovered. They are certainly not to be taken as diagnostic criteria, for

they may be found in many non-alcoholics, but they do serve in a measure as a fairly common factor among alcoholics. The importance of this factor lies in the fact that it gives some understanding of the behavior of the alcoholic. It therefore indicates an approach to dealing with the alcoholic, it indicates the attitude of the physician particularly toward establishing that rapport which is the first and most essential feature toward any successful therapy for the alcoholism of the so-called secondary addict.

It is not within my competence, nor is it of practical interest to the practitioner, to attempt any analysis of the basic forces operating to bring about the changes in the personality or character of the alcoholic. It is the clinical pictures only in which I am interested here. In its exhibition the change is one toward the essential egocentricity that so strongly characterizes the child. The alcoholic may be thought of as a child and may best be handled as a child. An appearance of grave respect, deep understanding, and broad tolerance with no recriminations, elicits confidence from the child—and from the alcoholic.

The development of the apparent retrogressive change in personality or character of the alcoholic is often slow. In the early stages of excessive drinking it is difficult to detect the beginning alcoholic from the occasional heavy drinkers who do not become alcoholics. In the face of difficulties the incipient alcoholic tends, perhaps, to drink more often than his associates and his drinking is more likely to reach the stage of drunkenness. As he drinks more, he develops a greater psychological tolerance to alcohol and large amounts may be required to give gratification. Eventually, as a possible turning point, he goes on his first spree of completely uncontrolled drinking. At first, sprees may be only occasional, but they tend to become more frequent, to occur from less and less provocation and to last longer. Gradually a compulsion to drink is developed, a spree tends to follow any drinking but periods of abstinence may still occur between sprees. At this stage after the spree, a deflated feeling is experienced, the enthusiasm and exuberance which were carried into earlier sprees and the vigor which was carried out of them is lacking. The alcoholic is tired, guilty, contrite, and, in his remorse, makes vows. But with the first subsequent drink, all responsibility to vows is disregarded. And preliminary to that drink, there is frequently a fairly definite prodromal syndrome. A psychic tension develops, the alcoholic is irritable, cranky, sour,

restless and jittery Only a drink will relieve this tension—and a drink means a spree

At this stage there is usually evidence of a type of thinking that shows, undisguised, the alcoholic's juvenile egocentricity He feels omnipotent but insecure He demands, and expects, that he shall be the center of interest He is sorry for himself and interprets even the most reasonable demands as thwarting him He wants to dominate He objects to routine and restraint His attitude may anticipate thwarting and be hostile, cynical, defiant At the same time he may exhibit for art, or beauty, or music, enthusiasms that are as exaggerated and unguided as those of a "bobby sock" crooner fan He senses a loneliness and isolation, a feeling of being apart and of the impossibility of being close to others To this he may over-react into complete isolation or, in contrast, to a fawning effort to ingratiate He promises to do better—he has learned his lesson—but his words carry only the responsibility of those of the temporarily frightened and contrite spoiled child In degrees greater or less, exhibited through the superficialities of a culture which is polished or crude, this is the patient with whom the practitioner must deal

If the attitude of the physician is understanding, tolerant, patient, serious, he may win the confidence of his patient and be able to help him Recriminations are useless, for the alcoholic has deep within him the strongest feelings of guilt and responds to them with hostility They are only further proof that no one understands him A high moral tone, preaching, drives him away The gift of really understanding the alcoholic, winning his confidence and cooperation, is often held in high degree by ex-alcoholics who act as lay therapists or group therapists as in Alcoholics Anonymous They have been through the same experience themselves, they know the feeling of tension, of discontent, of omnipotence, of guilt, and of resentment They know, and forgive, the inevitable "slips," after the spree, they are able to maintain their fully understanding attitude and an unabated confidence The physician, to be successful, must maintain the same confidence

There is no group of individuals—except children—who are more responsive to the attitude of the physician and sense his sincerity or lack of it more acutely than do alcoholics And, as I said in the beginning of this talk, it is the attitude of the physician and his depth

of understanding which may be the deciding factor in the recovery of the alcoholic, if he understands him and if he can make the members of the family and business associates likewise understand and cooperate, he has a good chance of steering the alcoholic toward recovery. Contrariwise, an adverse attitude, whatever its reason, may be, and may remain, the insurmountable obstacle to recovery.

I have also mentioned earlier that there are many different therapies of alcoholism. They are seemingly widely divergent in nature, but they have one element in common. It is the essential conviction of the possibility of recovery. The alcoholic will rarely recover under any treatment unless he believes he can recover and he wants to recover. One might go even further and say that if he can be so inspired to believe in recovery, he will recover under almost any kind of treatment if his confidence is carried over to the treatment and identified with it. It is, I think, the major function of the practitioner to inspire the desire and confidence and then select, at the necessary economic level, a therapy which he believes will be most suited to hold the respect of the patient.

In a recent article, Dr. Abraham Myerson has summed up the essential approach to successful therapy and also gives expression to a somewhat pessimistic view as to the specific virtue of any one particular method of treatment. He says: "The one common factor of all the therapeutics of alcohol addiction is embodied in the statement which is made by all therapists: *The patient must have the desire to be treated. He must wish to get well. He must be willing to cooperate.*" To these factors I should add the one which I have just discussed and which I think is equally important: *He must believe that he can get well.* Again, in this last respect the lay therapist who is an ex-alcoholic has a particular advantage, he not only speaks the alcoholic's language and knows his feelings, but he has been through it all himself and is there as a tangible example of the possibility of recovery.

In creating the will to recover it is usually essential to bear continually in mind the predominantly egocentric attitude of the alcoholic. The reason for recovery had best be made to stem from his own self-interests, his own ego, and not from family neglect and failure of duties which are topics prone to arouse undesirable emotional reactions. Something of this reaction, but in a most desirable direction, can sometimes be transferred to the alcohol itself by bringing it into

competition with his ego. He may believe, or pretend to believe, that he has control over his drinking, he is the master. If he can be made to see, and made to realize that others also see, that in reality he is not the master, that, in spite of his claimed omnipotence, he is the servant, his egocentricity may be turned to advantage as resentment against the alcohol, or as a fear of it. Again, a serious and dispassionate explanation by the physician of the probability of fairly rapid somatic deterioration as incidental to his heavy drinking, may arouse sufficient fear and yet provide an acceptable excuse for the desire to stop drinking.

Dr. Myerson, after stating the essential prerequisites to any successful therapy that I have given above, expands, as I have said, upon his doubts as to the specificity of any particular method. He says: "It may be that whatever method is used, if this will is present, if the desire to be free of alcohol addiction has reached that point of burning heat which James calls 'conversion,' it does not matter much whether benzedrine sulfate, which makes one feel good, or wine of ipecac, which makes one vomit, is utilized, it is of relatively little importance whether an exhorter does the trick by firing zeal through the fear of God or the friendly greeter of Alcoholics Anonymous is the agent of reform. The alkaloid strychnine will work as well, and no better, than the hormone insulin. In other words, the essential of all these therapeutic measures seems to be to enlist the cooperation of the patient, to galvanize his will, to bring about his conversion rather than to use any one specific measure."

What Dr. Myerson, as a psychiatrist, is saying, if I might rephrase his words in these possibly blunter ones of a physiologist, is the therapy of alcoholism is faith healing. The same, with equal bluntness, might be said of a good deal of psychotherapy. But even if it be true, I see no implication of belittlement. Physicians are prone to give a bad name to the whole conception of faith healing because they have come to regard this term in derogation from the early and even modern misapplication of this therapy to somatic diseases. Certainly the treatment of tuberculosis and broken legs by the laying on of hands and prayer deserves derision. But I do not think this derision should be inherent in the term "faith healing" when applied to the alteration of behavior habits. I doubt extremely whether faith has ever moved any mountains, but I know beyond doubt that it has moved

and is moving whole nations of men into patterns of behavior into habits for the maintenance of which they are willing to die I see nothing to be ashamed of in the statement that much of the therapy of alcoholism is faith healing and interpreting the rapport established between the patient and therapist as a feature common to all faith healing All that these statements signify is that there is no specific somatic—pharmacologic—therapy for alcoholism The important fact is that a great many alcoholics can be helped to recovery and to full rehabilitation

While I am not wholly in agreement, let us for the moment, to avoid argument, accept the baldest interpretation of the therapies as faith healing And you will remember that I have excluded from the handling of alcoholism those alcoholics who are symptomatic—psychotic—drinkers and those with extensive prealcoholic psychopathology The alcoholics to whom I am attempting to direct the attention of non-specialist practitioners are those of that group who, when their alcoholism is cured, their prealcoholic health and character restored, are, within a broad interpretation of the term, reasonably normal human beings They constitute the largest group of alcoholics and the majority cannot afford a long period of institutional care but must be treated, so to speak, as ambulatory We shall assume further that the practitioner has met them with a helpful attitude and carried out, with some success, his vitally important function of establishing the preliminary attitude toward treatment The patient is thus prepared for the therapy of his alcoholism The selection of the therapy falls upon the physician I have assumed, wholly for our argument, that the therapy is faith healing but a common designation does not mean that all forms which the healing may take are equally suited to the particular patient The therapy selected must be one that suits the patient one that he can believe in and will respect

The practitioner may decide that his patient will react best to the group fellowship of Alcoholics Anonymous, that he can be touched by proffered understanding and by actual aid in his "slips" and that he can be aroused to a deep desire and responsibility to help others If so the necessary contact should be made If on the other hand the physician feels that his patient does not have these qualities—perhaps a trifle sentimental in nature—he might turn to the one method best suited to the patient to whom a rational medical explanation would

make the strongest appeal, the so-called aversion or conditioned-reflex treatment. This method, which consists in the attempt to arouse an actual distaste for alcoholic beverages by the association of their taste with nausea and vomiting, possibly has a sounder physiological basis than faith healing only, but for it, the preliminary rapport is necessary, during it, a certain amount of suggestions, and after it, periods of reinforcement. If this forthright therapy, which perhaps makes its greatest appeal to the practical and hard-headed patient, seems also unsuited, there remains the individual, more expensive, and longer help of the psychotherapist who should be selected not only for his interest in alcoholism, but also for his personality.

At the danger of being unwarrantedly repetitious, I want to say again that the most essential step in any therapy of alcoholism is the initial contact—the part played by the practitioner. When his approach to the alcoholic is understanding and tolerant, something of the rapport is established, and when the practitioner is willing to listen, to advise, to talk to the family and help straighten out social difficulties, to be on the alcoholic's side, to guide him but not be exploited by him, he is himself carrying out the soundest and most helpful therapy of the alcoholism itself.

I have spent much time on what I have repeatedly called the physician's attitude and in so doing I have particularized. Now I want to generalize, to consider what forces have shaped the attitudes of the physician and too often shaped them to the detriment of the alcoholic. There is sometimes a tendency on the part of the members of our profession to feel that we are not only the inspirers for any broad social changes with medical implications but also the leaders who bring them into being. Sometimes I am led to wonder if this belief is justified. We all are products of the society in which we grow up, our fundamental views and beliefs on social matters, even those with medical implications are, I suspect, most often determined before we go into medicine. It is a chastening reflection that some of the greatest humanitarian social reforms built out of the potentialities of medicine were not seen or pioneered or led to social application by the physician. Sometimes they have even been obstructed by him. Often his attitude has been as bigoted as that of his non-medical neighbors.

I might illustrate this unfortunate fact with the rise and growth, a century ago, of an idea which is very pertinent to that held today

regarding alcoholism. You will recall that about a century and a half ago, Dr. Philippe Pinel advanced the idea that the symptoms of insanity might be ameliorated by humane care. To him, humane care meant the removal of manacles and chains and the discontinuance of torture. This therapeutic experiment aroused little interest among physicians. Half a century after his time there was no publicly supported institution in the United States for the care of the chronic insane. And, what was even more important, insanity was not considered by the physician as a disease in the sense that typhoid and smallpox were diseases. Insanity was felt to have in it a large element of plain human weakness, meanness and immorality—it was misbehavior for which the patient was in some measure, responsible. The laws of the period made perhaps a better distinction as to responsibility than did the public and the physician. The physician by and large, in dealing with the insane showed his impatience, his disgust, his dislike, he showed complete lack of understanding and sympathy. Probably he did not personally whip his patient or throw cold water on him, or chain him in a cellar but he directed and saw these things done. The deep sympathy and compassion that the physician had for the somatically ill did not flow over to the mentally ill, like the rest of the public he could find a cruel humor for their symptoms.

Then, as you will recall in the forties of the last century a Boston school teacher, Dorothea Linde Dix led the crusade that resulted not only in our tax-supported care of the chronic mentally ill but in an entire change in public attitude. The concept of mental illness carrying with it all the compassion formerly limited only to physical illness became the new view of the public—and of the physician is part of that public.

Today, the physician, brought up in the mores of the earlier decades of this century holds consciously or unconsciously many of what might be called pre-Dixian ideas in regard to alcoholism. And this view tends to be intensified by these features. First, the long preaching against the use of alcohol on the basis of morals, second, and quite opposite, the moderate and controlled personal use of alcohol by the physician, and third, the cruel attitude which sees in drunkenness on street, or stage, or radio, a subject of contempt or humor. The consequence is that the physician is sometimes prone to see the alcoholic as a man who deserves punishment—hence is in the

pre-Dixian days the drunk is usually a ward of the police court and his treatment a jail sentence and repeated sentences, he is prone to see the alcoholic as a man who cannot control a habit which in less degree he indulges in himself and therefore sees him in contempt for his weakness, he is prone to see the drunk as humorous or disgusting, and not as an ill man exposed to public derision but deserving sympathy and medical aid for the correction of his alcoholism, and last, he is a little prone, again sharing the public view, to believe that alcoholism is hopeless and the alcoholic not worth rehabilitating. It is such views, derived from the public of which the physician is a part, that have too frequently shaped the medical attitude toward alcoholism.

A fundamental social need today is in the development of the public opinion that alcoholism is a disease and that the alcoholic is an ill man deserving of the sympathy and care rightfully owing to an ill man. When public opinion—and in such matters public opinion often determines medical opinion—is so shaped, we will have made not only an humanitarian advancement but one of great practical importance toward the rehabilitation of the alcoholic and the prevention of alcoholism. Organized movements are already started which have among their purposes this shaping of public opinion, not in moral, but in medical and social channels, as part of the attack on alcoholism. Among these is our group and school at the Laboratory of Applied Physiology at Yale, with its affiliated National Committee for Education in Alcoholism, the Research Council on Problems of Alcohol, and the Committee on Alcohol Hygiene stemming from Johns Hopkins Medical School.

The problem of alcoholism is, even in its strictly medical implications, a large problem. Reliable statistics indicate that in the United States today there are some fifty-five million users of alcoholic beverages. The overwhelming majority of these men and women drink in a moderation that in no way endangers them. But some two million use these beverages to an extent that renders them liable to alcoholism. It is a small percentage perhaps, but it applies to a large number. Another half million have already become alcoholics to such a degree that they have impaired their physical and mental health. Any condition that threatens the health of two million people, and has already seriously affected the health of a half million, is a public health problem of important magnitude and one deserving the respect of the physician.

RECENT ADVANCES IN THE TREATMENT OF MALARIA*

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It will become increasingly important for the medical practitioner to be able to deal adequately with the malarias as increasing numbers of individuals are returned from hyperendemic malarious areas. Consequently a discussion of certain of the recent advances in the treatment of the malarias should be profitable at this time.

These improvements in therapy are not the result of the availability of new antimalarial agents, but rather are in consequence of the collection of information which permits a more rational and more effective use of those agents which are already available.

It is of general interest to note that the experimental approach that has led to these advances should be equally profitable when applied to other problems of therapy in man. In its essence it consists of the objective appraisal of the specific effects of a chemotherapeutic agent in relation to its concentration at a given site, in this case plasma; a quantitative evaluation of the physiological factors in the host which are of importance in the determination of such a concentration; and the use of these two types of information in the construction of rational regimens of therapy. This is not a new approach to problems in the field of chemotherapy. Rather, it is an extension to include the malarias, of the point of view which has facilitated the advances made in the treatment

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of bacterial diseases with the sulfonamides and penicillin. Actually the malarias in the human approximate the ideal for the application of this type of study.

A knowledge of the biology of the malarias will simplify the discussion of antimalarial agents, their uses, and their limitations. The underlying disease mechanisms have been clarified by recent work with some of the experimental avian infections¹ which appear to have somewhat similar characteristics to the human malarias. Malaria is acquired naturally when forms of the parasite known as sporozoites are introduced into the body incidental to the bites of infected anophelene mosquitoes. It seems likely that the sporozoites which are deposited locally are taken up by the tissue macrophages, whereas those which gain entrance into circulating blood, are taken up by other portions of the macrophage system of the body. Upon entry into a macrophage the sporozoite rounds up and undergoes rapid growth. This is followed by a series of segmentations, sporulations and reinvasions, which at this stage of the disease is presumably restricted to the macrophage system. This process covers a 6-7 day period, during which time the blood is devoid of demonstrable parasites.

At the end of this period certain of the tissue forms undergo another type of segmentation which results in the production of new forms of the parasite. These are capable of invading, growing and multiplying in the erythrocyte. Growth in the erythrocytes is accompanied by periodic segmentation, sporulation, and reinvasion of new erythrocytes in what is commonly called the schizogonous or asexual cycle of the plasmodium. The process continues with a progressive increase in the number of parasites in the blood until about 14 days after the day of the infection, in vivax and falciparum malaria, when a sufficient density of parasites is reached to precipitate the fever which is characteristic of clinical attack^{2a,b,d}. The duration of the incubation period in quartan malaria is of somewhat uncertain duration but is usually longer than that of vivax or falciparum malaria^{2c}.

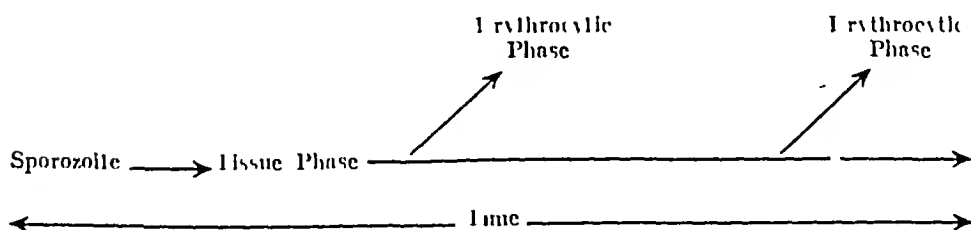
The subsequent course of the untreated disease is largely conditioned by the species of the plasmodium involved in the infection, and by the presence or absence of natural and acquired immunity. In the absence of immunity, and in the absence of chemotherapeutic intervention, falciparum malaria is characterized by a short, fulminating, and not infrequently fatal course, with little tendency towards true relapses.

subsequent to the termination of the initial period of clinical activity.^{2a} Vivax malaria is characterized by a longer initial course of clinical activity which, if untreated, frequently lasts more than 6 weeks, and by one or more relapses which may occur at intervals of a few weeks to several months.^{2b} However, contrary to falciparum malaria, vivax malaria, even if untreated, almost never results in a fatal outcome in the adult. Quartan malaria is characterized by a very long period of initial clinical activity and this is followed by infrequent relapses which may occur many years after the initial clinical attack.^{2c} The duration and severity of the clinical attacks in all three forms of malaria may be greatly lessened by proper treatment or modified by the presence of natural or acquired immunity.

The sexual forms of the parasite which are called gametocytes are derived from the asexual cycle of the erythrocytic phase of the disease.² These sexual forms are unimportant from the standpoint of the progress of the disease itself. However, they are of epidemiological importance, since they are responsible for the transmission of the disease from man to the anophelene mosquito.

It will further simplify a consideration of the problems of therapy if the mechanism of the true relapse in malaria is discussed at this time (see Figure 1). It seems likely on the basis of our present information, that relapses in vivax malaria result from the continued presence of underlying tissue forms of the plasmodium which persist well beyond the time of the establishment of the erythrocytic forms of the parasite which is responsible for the initial clinical attack. The continued presence of these tissue forms permits subsequent sporulations each of which may result in the re-invasion of the blood and, with the successful re-establishment of the erythrocytic forms, constitutes a discrete

FIGURE 1
MALARIA PARASITE CYCLE IN MAN



episode in the course of the disease. Should the development of immunity due to previous clinical activity be insufficient to curtail the multiplication of the new erythrocytic forms, then these may increase in number with the precipitation of renewed clinical activity characterized by both parasitemia and fever.

The normal course of falciparum malaria does not include numerous relapses as is the case with vivax malaria. This is presumably due to a lack of persisting tissue forms of the parasite very long beyond the time when the erythrocytic forms are first established. This is not to say that recurrent clinical activity within 3-4 weeks of treatment is unusual in falciparum malaria.^{2a} Such early renewals of clinical activity may be attributed to therapy which is insufficient to completely interrupt the asexual cycle of the parasite in the blood, rather than to the re-invasion of the blood from persisting forms of the parasite.

Little is known of the biological characteristics of quartan malaria in terms of the probable presence or absence of such tissue forms as a necessary factor in the production of true relapses.

It is apparent, from these considerations, that the malarias are characterized by a more complex disease mechanism, insofar as the etiological agents are concerned, than is true for most bacterial diseases. This fact acquires special significance when they are considered from the standpoint of the effectiveness of the various antimalarials available for use in treatment. It must be expected in any one of the malarias that each form of the parasite has somewhat different metabolic characteristics than the others. It may be concluded from this and the fact that the different forms may reside in different cell types of the host, that they will have varying susceptibilities to chemotherapeutic agents. In confirmation of the latter belief, experience has shown that, (a) quinine, the other cinchona alkaloids, and quinacrine are highly effective against the erythrocytic asexual and sexual forms of vivax and quartan malaria and against the erythrocytic asexual forms of falciparum, (b) plasmoquin is highly effective in the usual therapeutic doses against the sexual forms (or gametocytes) of falciparum and, (c) no drug is available that has been demonstrated to possess a significant action, at well tolerated dosage, against the sporozoites or primary tissue forms of any of the three common human malarias or against the persisting tissue forms of *P. vivax* which are presumed to be responsible for the relapses in infections due to the latter plasmodium.

The cinchona alkaloids and quinacrine, then, are useful in the termination of clinical attacks due to any one of the three important offending plasmodia. In addition, it is to be expected that these drugs in adequate doses will produce cures in falciparum malaria, but not in vivax malaria. Further, these agents are useful in preventing clinical attacks of malaria by suppressing the development of the erythrocytic phase of each of the malarials even though they exert no effect upon the sporozoite or upon the underlying tissue phases of the plasmodium. The usefulness of plasmoquin, on the other hand would appear to be limited to the rendering of patients with falciparum malaria non-infectious by virtue of its gametocidal action. The early promise of a second use, i.e., as an anti-relapse factor in vivax malaria, has not yet been fulfilled.⁷

QUINACRINE

The general usefulness of quinacrine in the control of malaria was not fully appreciated until recently. Certainly not at the time of the loss of our supply of quinine subsequent to our entry into the war.⁸ However, information has been developed which permits a more rational use of this important antimalarial.⁹ It has been possible to translate this information into specific schedules of therapy for use in the treatment and suppression of malaria.¹⁰ The therapeutic results with such a usage permit the conclusion that quinacrine has advantages over quinine or the other cinchona alkaloids in both the routine suppression and treatment of malaria.⁵

A discussion of the rational use of quinacrine requires the understanding that its antimalarial activity at any time is a simple reflection of its concentration in the plasma. As noted above, this is not a new concept of therapy, but a simple extension of the experience gained in the use of sulfonamides in bacterial disease to include the use of comparable agents in the treatment of malaria. However, it is not necessary to argue this point by analogy alone, since it has been established in a definitive fashion by experimental work with the human malarials.¹¹ A rational use of a drug in such a situation requires information on the factors which are concerned with its physiological disposition so as to clarify the relationship between drug administration and the plasma drug concentrations which are achieved and maintained on various regimens of therapy.

TABLE I

THE ABSORPTION AND EXCRETION OF QUINACRINE IN MAN

These data may be taken as typical of the results obtaining during and just after the administration of 100 mg of quinacrine dihydrochloride three times a day to a normal adult^a

<i>Day of Observation</i>	<i>Daily Quinacrine mgm</i>	<i>Plasma Concentration micrograms/L</i>	<i>Renal Excretion mgm/day</i>	<i>Fecal Excretion mgm/day</i>
1	300	36		
2	300	28		
3	300	82	4.8	30
4	300	48	5.5	7
5		87	7.3	36
6		17	3.3	10
7			8.0	6
8			2.2	11

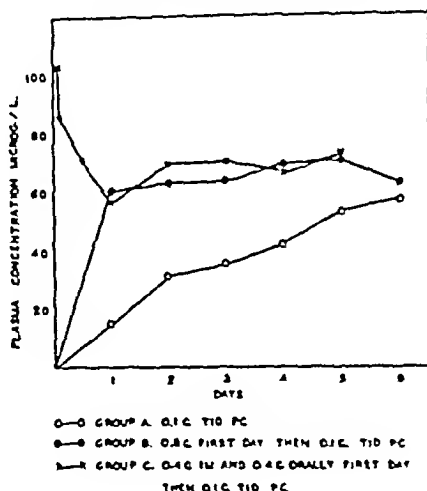
TABLE II

THE DISTRIBUTION OF QUINACRINE IN HUMAN BLOOD

These data may be taken as typical of the results obtaining during the administration of 100 mg of quinacrine dihydrochloride three times a day to a normal adult^a

	<i>Quinacrine Concentration (microg/liter)</i>
Plasma	89
Plasma water	8.9
Cerebrospinal fluid	5.4
Erythrocytes	117
Leukocytes	18,400
Whole blood	551
Plasma binding (per cent total)	90

FIGURE 2
VARIOUS QUINACRINE REGIMES
AND RESULTANT PLASMA CONCENTRATION



Physiological Disposition The plasma quinacrine concentration that obtains at any time on any regimen of therapy is determined by the dosage utilized, together with the net result of the operation of the processes of absorption, distribution, degradation and excretion.⁶

It is apparent from data in Table I that quinacrine is almost completely absorbed from the gastrointestinal tract and that the renal excretion of the drug accounts for very little of the daily dose. It may be concluded from these facts, and the fact that the plasma concentration becomes stabilized after several days of continued administration at constant dosage (see Figure 2), that the drug is mainly disposed of by the body by processes which result in its degradation.

Data which define the distribution of quinacrine in the blood are shown in Table II. The concentration of the drug in plasma, erythrocytes and leukocytes is in the order of 1, to 1, to 100-200. This excessive localization of quinacrine in the leukocytes requires special importance in studies which would assay the inherent antimalarial activity of the drug, or would delineate the factors concerned with its physiological disposition. Its concentration in whole blood at any time during a period of therapy is dependent as much or more upon the leukocyte count as upon the underlying chemotherapeutically active concentration in the plasma. It may be noted in passing that the major portion of quinacrine in the plasma is bound to the non-diffusible constituents in the plasma,

TABLE III

DISTRIBUTION OF QUINACRINE IN THE TISSUES OF A DOG

The dog received a daily dose of 20 mg per kilogram of quinacrine dihydrochloride daily for a period of 14 days prior to the experiment. The last dose was given 14 hours before the animal was sacrificed (wt 10.0 k).

	<i>Quinacrine Concentration (mgm/kg)</i>
Plasma	0.061
Muscle	55.0
Lung	310.0
Spleen	571.0
Liver	1306.0

presumably the plasma albumin. It would, perhaps, be more precise were studies of the physiological disposition of quinacrine, together with studies on its chemotherapeutic activity, related to the concentration of unbound drug in plasma water. However, this appears to be an unnecessary refinement at the moment.

The distribution of quinacrine in the body as a whole is described in outline form by the data in Table III. These data, collected in experiments on the dog, indicate that the drug may achieve concentrations in the liver and spleen as high as 10,000-20,000 times those concurrently observed in the plasma. A similar situation obtains in the human, as evidenced by experiments which derive the same type of information through indirect means. Thus, a major portion of the administered quinacrine is localized in the tissues of the body, leaving little in the plasma to exert a chemotherapeutic effect. It is in consequence of this that large initial doses of the drug must be given if one is to expect a high initial plasma drug concentration and an abrupt therapeutic effect. Furthermore, the extensive localization, together with the low rates of degradation (established by other types of experiments) and renal excretion, lead to a low rate of decline of the plasma quinacrine concentration, and consequently a low rate of the loss of the protection conferred by quinacrine, subsequent to the termination of drug administration.

Antimalarial activity * The response of well standardized and rigidly controlled blood induced vivax and falciparum malaria to various plasma levels of quinacrine has been utilized to assay the inherent antimalarial activity of the drug in terms of its ability to terminate or suppress the clinical attack. Blood induced malaria is best suited for such a study since it has the advantage of making available the simple erythrocytic phase of the disease.

It has been found in such infections that the *P. vivax* parasites⁹ are completely and permanently eradicated when plasma quinacrine levels of 30 micrograms per liter or more are maintained for not less than 4 days. Plasma quinacrine levels between 10 and 30 micrograms per liter generally produce temporary or partial effects and levels below 10 micrograms per liter produce little or no effect when maintained for a 4 day period. *P. falciparum* parasites⁹ appear to be more resistant and require approximately 50 micrograms per liter maintained for a 6 day period for complete and permanent eradication of the infection.

Recent work has shown that the erythrocytic phase of a mosquito induced vivax malaria⁹ has the same sensitivity to the chemotherapeutic activity of quinine as the blood induced infections detailed above. The figures just quoted, then, will have some significance when applied to naturally acquired malarias. Recent work⁹ also substantiates the previous belief that there are strain differences in susceptibility to the antimalarial activity of quinine and these differences may be expected to extend in certain instances to the antimalarial activity of quinacrine and other agents. However, the differences observed are not sufficiently great that the regimens of therapy given below will not, in general, terminate clinical activity.

The correlation between oral dosage and plasma quinacrine levels is poor⁹ so that it is difficult to state the antimalarial activity of the drug in terms of oral dosage. However, knowing the minimal plasma drug levels which are required to produce a given therapeutic effect and the range of plasma drug concentrations which are to be expected on a given dosage regimen in a group of individuals, it is possible to place the oral dosage sufficiently high for the maximal benefit to be derived from the drug for all but the exceptional individual.

⁹The blood induced and mosquito induced vivax malaria made use of specific strains of *P. vivax* which are purported to be off-shoots of the McCoy strain. While it is certain this is the case with the mosquito induced infections, cross immunity experiments have not as yet satisfactorily demonstrated that this is the case for the strain utilized in the blood induced infections. The falciparum malarias were induced by the inoculation of blood infected with the McClellan strain of *P. falciparum*.

Dosage schedules * It is with an understanding of these aspects of the physiological disposition and antimalarial activity of quinacrine that it is possible to establish rational regimens of therapy for both the suppression of the malarial and for the treatment of the clinical attack

The primary end to be sought in the treatment of the clinical attack is an abrupt termination of the clinical manifestations of the infection. The lower curve in Figure 2 represents the mean daily plasma quinacrine concentration of a group of individuals who received 0.1 g. of quinacrine three times daily, a dosage schedule commonly recommended prior to 1943.¹⁰ Very low plasma drug concentrations are achieved with such a regimen during the first two or three days of therapy because of the extensive localization of the drug in tissues. It is true that the plasma level increases progressively throughout the period of drug administration as more and more quinacrine accumulates in the tissue. However, because of the early low levels it is not to be expected that such a dosage will produce an early termination of clinical activity although, if continued for a period of days, plasma drug concentrations are achieved which will terminate the clinical attack. It is the delay in the initial effect of quinacrine, with such a dosage schedule, that led to the recommendation that quinacrine therapy be preceded by a 2 to 3 day course of quinine.¹¹

The situation is quite different when doses of quinacrine totalling 0.8-1.0 g. are administered during the initial day of therapy. This may be done by either the oral route or by a combination of intramuscular and oral administration (Figure 2). High plasma drug concentrations are obtained with either of these regimens during the initial 24 hours and may be maintained with the serial administration of 0.1 g. three times daily thereafter. It is to be expected from such plasma drug curves that a therapeutic effect will be apparent very early during the course of drug administration and in fact, such has been found to be the case.

These principles may be translated into simple dosage schedules for the administration of quinacrine. It is advised, in the routine treatment of malaria, that 0.2 g. doses of quinacrine be given at the time of the diagnosis of malaria, and at 4 hour intervals until a total of 1.0 g. has been given. Thereafter, it should be continued at a dosage level of 0.1 g. three times daily for a total period of 7 days.

* The dosage schedules listed are calculated for adults

More acutely ill patients, i.e., those with fulminating falciparum malaria, or those with nausea and vomiting, may be treated effectively through the use of intramuscular injections of quinacrine (Figure 2). It is not considered safe in either of these cases, to depend upon an exclusively oral route for the administration of drug. Very high and effective plasma drug concentrations are achieved within 15 minutes after the intramuscular injection of 0.4 g of quinacrine dihydrochloride.⁹ This is commonly given in two 0.2 g intramuscular injections, one into each buttock. Subsequent therapy may then be by the oral route if possible, or by the intramuscular route until oral therapy can be substituted. When oral therapy is utilized, subsequent to an intramuscular injection, it is advised that 0.2 g doses of quinacrine be administered at 4 hour intervals until a total of 1.0 g has been given by a combination of the two routes. Thereafter, 0.1 g is administered 3 times daily for a total period of 7 days. Should it be necessary to continue therapy by the intramuscular route, 0.2 g may be administered at 8 hour intervals until a total of 1.0 g has been administered then at 12 hour intervals until it is possible to begin oral therapy with 0.1 g three times daily.

It is to be emphasized that the indications for the intramuscular use of quinacrine are two, i.e., fulminating falciparum malaria, and clinical attacks of malaria in which the symptoms of nausea and vomiting are prominent. An additional word may be said in relation to the former of these two indications. Most clinicians in the past have used intramuscular or intravenous quinine in starting the treatment of fulminating falciparum malaria because it is known that this produces a rapid therapeutic effect. Intramuscular quinacrine has not been used to any great extent for such a purpose since it has not been appreciated that it may achieve an equally rapid effect. As noted above, very high and effective plasma quinacrine levels are found within 15 minutes of its intramuscular injection. The toxic hazard of intravenous injections of quinine is sufficiently great that it must be given slowly so that no advantage, with respect to time, is gained with the intravenous use of quinine as compared to the intramuscular use of quinacrine. The latter procedure has the additional advantage of simplicity.

Any one of the recommended regimens will produce plasma quinacrine levels in excess of those required to eradicate the trophozoites and effect an abrupt termination of clinical activity in any of the malarias.

in all but the exceptional individual. It is unusual for a patient to experience more than one subsequent paroxysm following the initiation of quinacrine therapy, providing adequate doses of the drug are administered.⁹ A cure of the disease is to be expected in the majority of patients with falciparum malaria, but not in the patients with vivax malaria. Most of the latter will experience a recurrence of clinical activity within one to 12 months. The number of such relapses which are experienced before the infection is cured is dependent upon many factors which will not be discussed at this time.

The use of quinacrine for the suppression of the malarias will not be discussed in detail since this is not a common problem for civilian practitioners of medicine in temperate climates. However, it should be appreciated that clinical malaria may be suppressed in all but a small proportion of individuals during months of exposure to malaria by the weekly administration of 0.6 to 0.7 g. of quinacrine. This dosage, in most individuals, will result in plasma quinacrine levels known to have significant action on the erythrocytic phase of the malarias. Unpleasant gastrointestinal reactions were encountered when quinacrine was administered in the earlier recommended doses of 0.2 g. twice weekly.^{10,11} However, these reactions are minimized and a therapeutic advantage gained when a larger total weekly dosage is administered in small daily doses of 0.1 g. given after meals. Suppressive therapy of this type is commonly continued for a three-week period after the last exposure to malaria. This may be expected to accomplish cures of the suppressed falciparum malaria, but not of the suppressed vivax malaria. Clinical activity due to the latter will appear in most infected individuals within a few weeks to some months later. The time elapsing apparently depends upon many factors not well defined, among which are included the strain of the offending organism, and perhaps the number of strains involved in the infection, together with the density of the underlying tissue phase of the infection.

The delayed primary attacks which occur when clinical activity is suppressed at the time of the expected initial attack, as well as the clinical relapses, may be treated in much the same fashion as has been described above for the primary attacks. In general, the relapses or recrudescences of clinical activity respond more quickly to treatment than the primary attack, due to presence of some acquired immunity.

Some consideration must be given to the individuals who, subsequent

to an extensive exposure, develop vivax malaria which is characterized by innumerable relapses occurring at short intervals. These patients do well when maintained on suppressive therapy for a period of several months, perhaps six, following the treatment of any given acute attack. Actually, there is little information on the ultimate effect of this type of continuation therapy. Its rationale depends upon the assumption that the tissue phases of the plasmodium must progress through their normal life expectancy and that this will take place whether the erythrocytic phase of the disease and its accompanying clinical symptoms are, or are not, suppressed. The suppression of the erythrocytic phase of the disease permits an individual to pursue a normal life during the infection and should not, per se, prolong the course of the disease.

QUININE AND THE CINCHONA ALKALOIDS

It is not necessary to spend much time in a discussion of the use of quinine, the cinchona alkaloids or totaquine, in the treatment of malaria, since it is unlikely that any of these preparations will be used extensively by physicians in this community. It is important to appreciate that any one of these may be utilized for the same purposes as have been described above for quinacrine. Recent work has confirmed the belief that the cinchona alkaloids other than quinine, i.e., cinchonine, cinchonidine and quinidine, have an antimalarial activity which is roughly the equivalent of quinine.⁹ It is to be expected that the combination of these alkaloids in the form of a standard product such as Totaquine, USP, will also have roughly the same antimalarial activity as quinine. The dosage of totaquine as compared to quinine should be based on the alkaloid content of the preparation used.

The use of the cinchona alkaloids in the suppression and treatment of malaria differs from the use advised in the case of quinacrine, largely because the cinchona alkaloids are not localized as extensively in the tissues. However, the less extensive localization, together with more rapid rates of excretion and degradation, results in a rapid fall in plasma levels of the cinchona alkaloids when oral dosage is stopped. Consequently, relatively lower initial doses, as compared to the maintenance doses, are required to produce the desired result.

Quinine, of course, is a highly effective antimalarial agent. However, its antimalarial activity is less than that of quinacrine when the latter is properly used.⁸ It was noted above that the effective 4 day plasma

concentration of quinacrine for vivax malaria due to a well standardized strain of *P. vivax* is 30 micrograms per liter. The effective quinine level, determined in the same way and on the same strain, is found to be 5 mgm per liter. Inherently, i.e., based on the plasma concentrations required to produce a given therapeutic effect, quinacrine is almost two hundred times more active than quinine. The pharmacology of the two drugs, however, is such that, relative to the oral dose, lower plasma levels are achieved with quinacrine than with quinine. But still, the required oral maintenance dosage of quinacrine is considerably less than that of quinine. In addition, quinacrine plasma levels that are many times in excess of those required for an adequate therapeutic effect may be achieved without particularly toxic hazard, while the margin of safety with quinine is somewhat less.

The maximal benefit to be derived from quinine, in the treatment of the clinical attack, should be obtained by the administration of 3 grams of one or another of the available salts of quinine during the initial day of therapy, followed by 2 g daily in divided doses. Therapy may be limited to a 7 day period in vivax malaria, and perhaps to a 10 day period in quartan and falciparum malaria. Patients with fulminating falciparum malaria, or those in whom nausea and vomiting are prominent symptoms, can receive quinine intravenously during the initial stage of therapy. This is commonly administered by slow intravenous infusions, single doses not to exceed 0.5 g, total dosage to be administered each day being the same as that advised for oral therapy. Again, oral should supplant parenteral therapy at the earliest possible time. The intramuscular use of quinine is contraindicated because of the not uncommon occurrence of necrosis at the site of the injection.

For suppressive purposes, it is necessary to administer as much as 1 g of a quinine salt daily to approach a therapeutic result which is comparable to that which obtains when 0.1 g of quinacrine is administered daily. Unpleasant side reactions are to be expected in a fair proportion of individuals carried on such a dosage regimen for any length of time. In addition it is less certain that suppressive quinine, used in accordance with these directions, will effect cures of the suppressed falciparum malaria. Consequently there would appear to be little question that quinacrine is the drug of choice, among those now available, when a suppressive therapeutic effect is desired.

PLASMOQUIN

Plasmoquin is advised in only one instance, i.e., to render a patient with falciparum malaria non-infectious to mosquitoes. It is commonly advised that plasmoquin be administered at a dosage of 10 mg three times daily for a total period of 5 days.¹ However, such a regimen may be expected to produce toxic symptoms in a proportion of individuals and the consequence of such reactions may be serious. These may include the development of methemoglobinemia and moderate to severe disturbances of the gastrointestinal tract. However, the most serious toxic hazards are those which follow the occurrence of intravascular hemolysis. These reactions usually do not appear until the 4th or 5th day and therapy may be limited to three days without sacrificing the therapeutic benefit which is to be derived from plasmoquin administration.

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CARDIAC ENLARGEMENT ITS RECOGNITION AND SIGNIFICANCE

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IT HAS long been an accepted aphorism that an enlarged heart is a diseased heart. It might be well to preface our discussion with a few brief remarks as to why enlargement of the heart is unfavorable to the body economy. The physiologically dilated or hypertrophied heart may function with mechanical efficiency but it is important to recognize that the true measure of cardiac, or more properly circulatory, efficiency is the energy expenditure of the heart in maintaining its circulatory output, and not merely the ratio of the oxygen consumption to the kilogram-meters of actual work performed.¹ This distinction, i.e., the concept of efficiency of the circulation versus the mechanical efficiency of the heart muscle, is important for it helps to explain why cardiac enlargement betokens impaired reserve. Work expended against increased arterial resistance or to compensate for valvular defects is wasted in so far as the function of the heart to maintain its cardiac output is concerned. Since oxygen consumption is proportional to fiber length, or diastolic volume, the cardiac output is maintained by the dilated or hypertrophied heart with greater energy expenditure, hence efficiency is decreased. Hypertrophy and dilatation as a rule are closely associated so that when the heart is enlarged, some degree of dilatation of the cardiac chambers is usually present.

Beyond indicating the presence of disease the recognition of cardiac enlargement provides valuable information as to the type and the extent of the lesion, for characteristic changes frequently occur in various types of heart disease. Accurate estimation of the size of the heart, therefore, is most important.

Methods for studying the size of the heart include physical examination and techniques employing the Roentgen ray and the electrocardiograph.

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It is with no intent to depreciate the importance of physical examination that we point out that there are serious limitations to inspection, palpation and percussion, particularly when the chest wall is muscular or obese, or in the presence of pendulous breasts or emphysema. Enlargement of the cardiac chambers other than the left ventricle cannot be detected on physical examination except in advanced stages.

It has long been recognized that characteristic electrocardiographic patterns occur with enlargement of the various chambers, but this aspect of electrocardiography has received relatively little attention. Recently we conducted a study to establish specific electrocardiographic criteria of left ventricular hypertrophy² and we found, employing these criteria, that the electrocardiogram provides the most sensitive method for detecting hypertrophy of the left ventricle, frequently exhibiting definite abnormal patterns where the roentgenologic findings are normal. Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following changes:

- 1 Increase in amplitude of the QRS complex, best expressed by the sum of R_1 and S_3 . Hypertrophy is present if this sum exceeds 2.5 millivolts and is probably present if it is over 2.2 millivolts. The increase in voltage is the earliest electrocardiographic change in hypertrophy.

- 2 Any perceptible depression of the S-T segment in lead 1, even of as slight degree as 0.5 mm (0.05 millivolts).

- 3 Lowering of T_1 below 1 mm or further degrees of abnormality of T_1 .

The changes in the S-T segment and the T wave may develop in the absence of left axis deviation, and left axis deviation is not an invariable or necessarily integral part of the electrocardiographic pattern of left ventricular hypertrophy. We found that the usual occurrence of left axis deviation in hypertension is due largely to a transverse position of the heart, which in itself causes left axis deviation. In slender subjects with left ventricular hypertrophy left axis deviation is not so often observed.

In advanced stages of hypertensive heart disease the characteristic electrocardiographic pattern approaching left bundle branch block is often observed. It must be emphasized that this is a late phenomenon and that employment of criteria such as we have proposed makes it possible to recognize left ventricular hypertrophy in its incipient stages.

The electrocardiographic patterns of left ventricular hypertrophy are of considerable prognostic importance. Thus, in a recent mortality study in hypertension³ we found that there was a distinct increase in mortality with progression in the electrocardiogram toward an abnormal pattern. The life expectancy among those with the pattern of left ventricular hypertrophy was about half that of subjects with identical blood pressure readings in whom the electrocardiograms were normal.

A characteristic electrocardiographic pattern occurs with hypertrophy of the right as well as of the left ventricle. The changes consist of right axis deviation, accompanied by depression of the S-T segment in lead 3 and frequently lead 2, and inversion of the T wave in lead 3 and eventually in lead 2 as well. The voltage of the QRS complex is not regularly increased as it is with left ventricular hypertrophy. When the pattern is fully developed it is quite characteristic of right ventricular hypertrophy, but frequently in the less advanced stages it may be difficult to be certain that right ventricular strain is present because similar changes may occur in normal subjects of slender build, or as a result of positional changes of the heart.

Auricular enlargement, also, may be revealed in the electrocardiogram. The left auricle is the one which is usually enlarged, most often because of mitral stenosis. Changes occur in the P wave as a result of impaired conduction through the dilated and hypertrophied auricle. The P wave becomes notched, its duration exceeds 0.10 seconds, and it increases in amplitude to more than 0.25 millivolts. Ultimately, auricular fibrillation ensues as a result of longstanding auricular enlargement. Auricular premature beats and auricular flutter occasionally presage the change to auricular fibrillation.

Although hypertrophy of the left ventricle may often be detected earlier in the electrocardiogram, roentgenologic methods are superior in revealing auricular and right ventricular enlargement. When generalized cardiac enlargement is present the electrocardiographic changes are less specific, and the opposite effects of right and left ventricular enlargement may balance each other so that there is no deviation of the electrical axis, although other abnormalities, such as increased voltage and changes in the S-T segment and T waves tend to persist. The electrocardiogram may be relatively normal when enlargement is caused by dilatation of the cardiac chambers rather than by hypertrophy. Roentgenograms, therefore, are superior when generalized enlargement exists.

Roentgenologic methods for the recognition of cardiac enlargement include fluoroscopy, orthodiagraphy and teleoroentgenography

Fluoroscopy, technically the simplest of roentgenologic procedures, as well as the most generally available, provides the greatest information and should be carried out routinely as a preliminary to further roentgenologic study. In any study of the size of the heart an attempt should be made to describe enlargement in terms of the individual chambers, for characteristic changes occur in various types of heart disease. For this purpose fluoroscopy is of particular advantage because the contours of the separate chambers may be inspected in their entirety by rotating the subject into oblique positions, and their limits ascertained by observation of the pulsations. Adequate visualization of all the chambers is afforded by making roentgenograms in the posteroanterior, left anterior oblique (50° to 55°), and right anterior oblique (50° or over), or right lateral, position. Examination in the latter view is aided by outlining (not filling) the esophagus with a thick barium mixture, for the esophagus is in close relation to the posterior surface of the heart, particularly the left atrium. The relation of the chambers of the heart to adjacent mediastinal structures, such as the esophagus, bronchi, and chest parietes, which can be ascertained by study in the oblique positions, is of great value in establishing whether or not enlargement is present. Thus, early enlargement of the left atrium is indicated by indentation and retrodisplacement of the esophagus, and also by upward extension of the left atrial contour toward the left main bronchus, obliterating the infrabronchial space.⁴ Eventually, the left bronchus becomes elevated and even compressed, but this is a later sign. The right ventricle forms the anterior surface of the heart, and, when it is enlarged, extends forward toward the anterior chest wall, narrowing the precardiac space, this is best revealed by study in oblique positions. Enlargement of the right ventricle is indicated indirectly in the frontal view by prominence of the upper left and of the right heart borders.

Fluoroscopy is not well suited for absolute measurement of the heart size since there is considerable magnification of the heart image due to divergence of the x-ray beam resulting from the short tube-film distance usually employed in fluoroscopic examination. The degree of magnification depends, not only on the tube-film distance, but on the object-film distance, as well. Magnification is, accordingly, greater in subjects with deep chests, in whom the heart contours are further removed from

the film, than in slender subjects and children

Magnification can be obviated on fluoroscopy or in roentgenograms by a simple procedure.⁵ A lead scale placed vertically parallel to the cassette alongside the subject in the plane of the anterior axillary line is magnified exactly in the same proportion as is the heart silhouette. The scale is recorded with the heart in the same exposure of the fluoroscopic screen or roentgenogram and serves as a reference scale for measurement of the heart size. This procedure is equally suitable for 35 mm or 4" x 5" photographs of the fluoroscopic image, a technique which is being increasingly employed, particularly in surveys in the armed forces and industry.

Projection distortion of the heart in fluoroscopy also may be obviated by the orthodiagraphic technique. Only the central ray of the fluoroscopic beam, whose position is indicated by a small lead marker, is used to trace the outline of the cardiac contour. The screen and patient being fixed, the central ray is moved along the cardiac contour by moving the tube with the left hand, while the right hand follows the lead marker along the heart border recording numerous points at about one centimeter intervals. Orthodiagraphy requires training and exact application and does not appear to possess any advantage over the simpler lead scale method we have described which may be applied conveniently during fluoroscopy to obtain exact measurements of the cardiac shadow.

Roentgenography possesses the advantage over fluoroscopic techniques of providing an objective and permanent record, not only of the heart, but of the pulmonary fields as well, which are of interest and importance in the diagnosis of heart disease. At two meter (6.5 feet) tube-film distance (teleoroentgenography) the magnification of the cardiac image due to divergence of the x-ray beam is reduced to the order of 5 per cent, this does not increase appreciably until the tube-film distance becomes less than 150 cm (5 feet).

Apart from the projection distortion there are numerous other pitfalls in interpretation of roentgenograms of the heart. The size, shape and position of the heart are influenced by certain physiological variables and technical considerations, which should be appreciated before deciding whether the heart is pathologically enlarged. It is important that the subject be centered properly, which can be recognized in the roentgenogram by an equidistance of the inner borders of the clavicle

from the midpoint of the vertebral spine. The tube should be at the level of the third anterior intercostal space. Even slight degrees of rotation may significantly alter the size of the cardiovascular shadow, particularly the aortic arch silhouette. The exposure should be made in the erect or sitting position, and with respiration suspended in ordinary inspiration since extremes of respiration or straining may cause marked variations in the size of the heart. The size of the cardiac shadow varies considerably depending on the phase of the cardiac cycle in which the exposure is made. When the pulsations are vigorous the transverse diameter of the heart may vary by as much as 1.5 to 2 centimeters from systole to diastole. Since diastole is longer than systole at ordinary heart rates, roentgenograms are more often exposed in diastole. It is not true as is widely supposed that a full second exposure lasting through a complete cardiac cycle will record the diastolic or largest heart shadow.⁶ It has been shown, in fact, that the border of the heart in long exposures lasting through the complete cardiac cycle more closely approximates the systolic, or smallest, heart size. Prolonged exposures thus serve no advantage and not only give an indistinct cardiac outline but blurred hilar structures as well due to transmitted motion from the cardiac pulsations. Several devices employing pulse waves, heart sounds, and the electrocardiogram have been contrived to permit exposure at selected phases in the cardiac cycle. The technique of roentgenkymography makes it possible to register one or several complete cardiac cycles on a single film and provides a record of the cardiac outline both in systole and diastole.⁷

Several anatomical peculiarities may cause confusion in interpreting the cardiac shadow. The most important is an extra-pericardial fat pad which merges with the lower left heart border and which may obscure the apex. The margin of the fat pad must not be mistaken for the left heart border which may be discerned within the fat pad, particularly if the roentgenogram is made with slightly over-penetrated technique. Skeletal abnormalities of the thorax, such as funnel chest and kyphoscoliosis, by displacing and distorting the heart occasionally may render difficult the accurate determination of the size of the heart. The dextroscoliotic spine may simulate the right heart border or ascending arch of the aorta, and a diagnosis of cardiac enlargement or dilatation of the aorta may thereby be made erroneously. The size, shape and particularly position of the heart may be altered in pulmonary diseases

such as fibroid phthisis, atelectasis, pneumothorax, etc., and by diaphragmatic hernia or elevation of the diaphragm as in pregnancy and ascites

Several measurements such as those of Vaquez⁸ and Fray⁹ have been proposed which purport to serve as criteria for enlargement of the individual heart chambers. The value of such measurements is, at best, limited. Attempts to measure the cardiac chambers separately are necessarily inexact since only one border is visualized, the shadows of the various chambers merging to form the cardiac silhouette. The relation of the heart to adjacent structures, such as the esophagus, bronchi and thoracic parietes, determined by fluoroscopy and teleoroentgenogram study in posteroanterior and oblique positions as already indicated, is of greater value than mensuration in detecting enlargement of the individual chambers.

Measurements are of greater value as an index of generalized enlargement of the heart than in determining the size of the individual chambers. There is a definite field of usefulness for measurement standards in evaluating enlargement of the heart as a whole since very often enlargement does not involve individual chambers distinctly and one can state only that the heart is enlarged. Mensuration is unnecessary when gross enlargement exists, but lesser degrees of enlargement often escape detection on inspection. Conversely, an apparently large cardiac shadow may assume less significance when it is considered in relation to standards of body build. If proper account is taken of the physiological variables which influence the size of the heart, mensuration is a valuable aid in determining whether the heart is enlarged. Measurement is helpful also in comparison of changes in heart size in serial examinations in the same subject. Another field where measurement has found wide application is in physiological and pharmacological investigations of the heart.

Several physiological factors may influence the size of the heart and these must be recognized and considered in evaluating measurements. Body build has a most important determining influence on the size of the heart. The correlation of heart size with various factors, such as weight, height, surface area, muscular development, thoracic circumference and other thoracic measurements, etc., has been probed extensively. The dependence on weight is somewhat greater than on height but the correlation is improved if both weight and height are considered. A $\frac{\text{weight}}{\text{height}}$ index has been evolved which appears to serve as a

satisfactory coefficient for prediction of normal standards. The influence of sex, and of age in adults, on the size of the heart is relatively small compared with the factors of weight and height, and for practical purposes may be disregarded in prediction standards.

Of the many measurements that have been advocated the best known are the transverse, longitudinal and broad diameters. These few simple measurements suffice to determine whether the heart is enlarged. The transverse diameter, and the area of the frontal cardiac silhouette, which may be determined from the long and broad diameters, as we will presently show, are the most thoroughly tried and standardized and among the best of all measurements.¹⁰ In addition, the heart volume, which is of great physiological interest, can be accurately calculated from these diameters.

The simplest, most widely employed, and one of the most useful measurements is the transverse diameter, which is the sum of the greatest extension of the right border to the right, and of the left border to the left, of the midline. The cardiothoracic ratio, which is predicated on the assumption that the transverse diameter should be less than half the transverse diameter of the chest at the level of the diaphragm, has been widely popularized, but is crude and inexact. The width of the thorax is only a rough index of body stature, and is altered in any given case by respiration, and also in pathologic conditions, such as emphysema. Ordinarily the transverse diameter of the heart is considerably less than half the transverse diameter of the chest, so that appreciable enlargement may escape detection if this ratio is employed as an index of the size of the heart. More accurate standards, based on weight and height have been established both for the orthodiagram by Hodges and Eyster¹¹ and for the teleoroentgenogram by Ungerleider and Clark.¹² Teleoroentgenographic standards are slightly greater than those for the orthodiagram, so that it is not proper to use the orthodiagram values in reading teleoroentgenograms. Because of the increasing employment of the teleoroentgenogram, a new prediction table, based on a study of 1,460 teleoroentgenograms of normal subjects, was prepared, and this should be employed, rather than the older orthodiagram standards, when reading teleoroentgenograms.

The actual transverse diameter should not be interpreted too strictly in relation to the predicted value, for there are appreciable physiologic variations in the size of the cardiac shadow in addition to changes due

to the phase of the heart cycle and respiration. Diameters which are more than 10 per cent above the predicted value should be regarded as abnormal, and the heart may be considered as almost certainly enlarged if the transverse diameter is over 15 per cent in excess of the predicted diameter, since less than three per cent of normals exceed this limit. An increase in the transverse diameter is most often caused by enlargement of the left ventricle, but enlargement of any of the cardiac chambers, even of the left auricle, when it forms the right border of the heart, can widen the transverse diameter.

The utility of the transverse diameter employing our tables has been confirmed in several studies. The conclusion of Comeau and White in their article entitled *A Critical Analysis of Standard Methods of Estimating Heart Size from Roentgen Measurements*,¹¹ may be quoted:

"1. A comparison of transverse heart diameters, frontal cardiac area, and heart volumes in 200 normal hearts leads us to conclude that the transverse diameter of the heart compares favorably with the other actual heart measurements and is the most satisfactory from the clinical standpoint.

2. We believe that the cardiothoracic ratio is not sufficiently reliable to warrant the wide usage which it now enjoys and that it should be discarded in view of the fact that it has been superseded by a more accurate and an equally simple correlative method.

3. We have found that the prediction tables offer the best approach to the problem of determining whether cardiac enlargement exists in an individual case. Our results indicate that the use of the transverse heart diameter and its deviations from the predicted normal is as yet the most reliable and the most applicable clinically of the existent methods."

Recently an important study was carried out by Sherman and Ducey¹⁴ in which a direct comparison was made between the weights of the heart at autopsy in 200 adult males, and three types of measurement, the Ungerleider and Clark transverse diameter prediction table, the Newcomer heart-lung rectangle method and the cardiothoracic ratio. Their findings were reported as follows:

"The values obtained by the Ungerleider method more closely approximate the enlargement by weight than do those by the other two methods, particularly in borderline cases. The Ungerleider method is the only one of the three by which enlargement of 40

per cent or less can be detected. There is constant correlation between the percentage deviation of the transverse diameter, as obtained by the Ungerleider method, and the percentage deviation in heart weight."

Two other diameters, the long and broad diameters, are well known, although these are somewhat less valuable individually than the transverse diameter. The long diameter extends from the junction of the cardiac and vascular silhouette on the upper part of the right border of the heart obliquely downward to the apex on the left. This diameter, which is approximately ten per cent greater than the transverse diameter, is increased chiefly as a result of left ventricular enlargement. The broad diameter is the greatest diameter perpendicular to the long diameter. The broad diameter is often drawn as the sum of the two perpendiculars from the long diameter to the lower right and upper left heart borders, but properly it is the greatest single diameter from upper left to lower right heart border perpendicular to the long diameter. If the heart is placed transversely, it may be necessary to extend the lower part of the right border slightly below the diaphragm in its natural curve in order to delineate the limit of the broad diameter. The broad diameter averages about 15 per cent less than the transverse diameter.

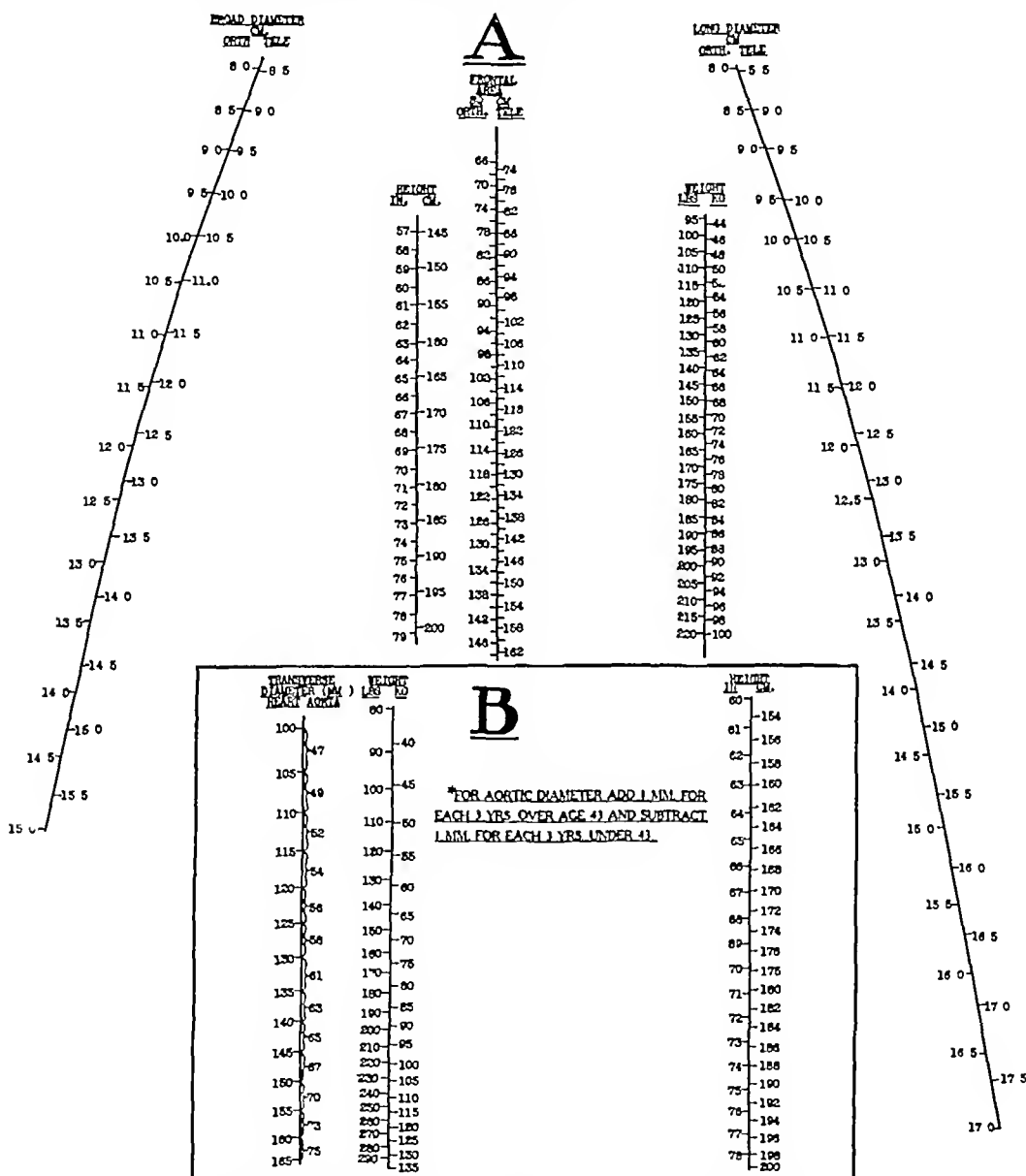
The long and broad diameters are of interest, not so much by themselves, but for their product, i.e., the frontal cardiac area, which is an expression of the two-dimensional size of the cardiac shadow.

The area of the frontal cardiac silhouette in relation to standards based on weight and height has been widely recommended as an excellent criterion of the size of the heart. In order to ascertain the area of the frontal silhouette, the upper and lower limits of the heart shadow must be completed by arbitrary and imaginary lines, and this requires considerable experience to attain duplicable results. The area is measured by means of a planimeter, or by counting squares within the area on cross-section paper. In orthodiagraphic examination, observation of the pulsations helps in outlining the upper and lower limits of the heart contour. In the teleoroentgenogram, however, the error in completing the upper and lower borders is much greater, and, for this reason, satisfactory frontal area measurements have not hitherto been obtained from the teleoroentgenogram, although this method yields excellent results in orthodiagraphy in the hands of those who are well trained in the technique. Inasmuch as the cardiac shadow is ellipsoid in shape, its area may

Nomograms for Area and Transverse Diameter of frontal heart silhouette

A PREDICTED AREA FROM WEIGHT AND HEIGHT¹ AND ACTUAL AREA FROM LONG AND BROAD DIAMETERS ($A = \frac{\pi}{4} L \times B$) FOR ORTHODIAGRAM AND TELEORÖENTGENOGRAM

B TRANSVERSE DIAMETER OF HEART² AND AORTIC SILHOUETTE³ PREDICTED FROM WEIGHT AND HEIGHT FOR TELEORÖENTGENOGRAM



THE VALUES FOR ACTUAL (OR PREDICTED) AREA ARE READ AT THE POINT AT WHICH A STRAIGHT LINE EXTENDING FROM THE LONG AND BROAD DIAMETERS (OR WEIGHT AND HEIGHT) INTERSECTS THE CARDIAC AREA SCALE. ORTHODIAGRAM VALUES ARE ON THE LEFT, TELEORÖENTGENOGRAM VALUES ON THE RIGHT. IN THE LOWER NOMOGRAM THE PREDICTED TRANSVERSE DIAMETER OF THE HEART (LEFT SIDE OF SCALE) OR AORTIC ARCH (RIGHT SIDE OF SCALE) IS OBTAINED AS AN EXTENSION OF A STRAIGHT LINE CONNECTING HEIGHT AND WEIGHT. A CORRECTION FOR AGE, AS INDICATED, IS NECESSARY FOR THE AORTIC DIAMETER.

be calculated from the product of its axial long and broad diameters (area of ellipse $= \frac{\pi}{4}$ long \times broad diameters) Calculation of the cardiac area by means of the formula, $\frac{\pi}{4}$ long \times broad diameters, yields values which correspond very closely to the actual area, as measured by planimetry (within three per cent) This product may, therefore, be used to estimate the cardiac area in lieu of planimetry¹⁰ This is of particular advantage in the teleoroentgenogram because the long and broad diameters can be measured accurately, whereas the planimetric estimation of the cardiac area is less accurate The product $\frac{3}{8}$ long \times transverse diameters, approximates the cardiac area, but is less satisfactory than the product of long and broad diameters, for the mean deviation from actual areas, as ascertained by planimetry in 134 orthodiagrams, was found to be seven per cent, whereas with the long and broad diameter product the mean deviation in the same group of 134 cases was less than three per cent The actual cardiac area should not exceed ten per cent over the predicted value, and, if it does, the heart may be considered enlarged Recently we prepared a nomogram for prediction of the cardiac area from weight and height, and actual area as calculated from the long and broad diameters (Figure 1) The nomogram permits the frontal area to be read directly without calculation from the long and broad diameter measurements Predicted values for the frontal area based on weight and height are indicated in the same nomogram chart on another scale

The validity and usefulness of the nomogram for frontal area has been confirmed by Kurtz¹⁵ on the basis of 155 cases tested Kurtz reported, "This relatively close approximation to the planimetric area indicates that the method has a practical application of distinct value in the great majority of cases" He states further, "Most cardiologists will admit that the cardiothoracic ratio is the poorest roentgenographic method of detecting cardiac enlargement, whereas orthodiascopic measurement of the frontal area of the cardiac silhouette is probably the most accurate The latter has the obvious disadvantage of requiring a considerable amount of training in the technique If the other disadvantages of measuring the frontal area, namely, the completing of the upper and lower borders and the use of a planimeter, could be obviated, one would have an ideal method for even the untrained The method proposed by Ungerleider and Gubner approaches the ideal"

To summarize our discussion of cardiac measurements, it is evident that with the use of either or both the transverse diameter and the nomographic determination of frontal area, we have two simple and accurate methods, which suffice to determine whether cardiac enlargement is present

Roentgenologic examination of the heart should invariably include observation of the aorta, for abnormalities such as widening, tortuosity, and calcification occur frequently in heart disease, particularly in hypertensive and arteriosclerotic heart disease and in syphilis. Measurement of the true caliber of the aorta is difficult because both contours are not visualized in the frontal position. The left border of the descending aortic arch is visualized in the frontal roentgenogram, and, if the esophagus is filled with barium, the right border of the aorta is indicated by the aortic indentation of the esophagus, therefore, the diameter at this level of the aorta can be ascertained by subtracting 2 mm representing the thickness of the esophageal wall (Kreuzfuchs' method)¹⁶. The method is not dependable when the aorta is tortuous and the aortic knob projects to the left. Where a portion of the aortic knob is distinct, as is usually the case in adults, the true diameter of the aorta at this level may be ascertained by the simple method we have proposed,¹⁷ of completing the circle, of which the aortic knob is an arc, by means of a compass. The caliber of the aorta determined by this simple procedure checks exactly with the diameter obtained by visualization of the aorta in the left anterior oblique position and with the Kreuzfuchs' method. The diameter of the transverse arch of the aorta can frequently be measured directly in the left anterior oblique position, particularly when some degree of emphysema is present to aid contrast, or when overpenetration technique is employed. The diameter of the aorta at this level averages 3.0 to 3.5 cm in adults, varying from 2 to 4 cm depending on body build and age.

These methods indicate the size of the transverse and descending aortic arch, but it is the ascending aorta which is most often enlarged in disease. The first portion of the ascending aorta is buried in the cardiac shadow, and cannot be studied by any means except contrast visualization with diodrast. The diameter of the ascending aorta just above the aortic valve normally is 25 per cent greater than the diameter of the transverse arch at the level of the aortic knob. The ratio does not hold in pathological states as the ascending aorta usually becomes dilated to

a much greater degree than the transverse or descending arch. Enlargement of the ascending aorta is evidenced by prominence of the right border of the vascular pedicle and by a forward bulge of the anterior border of the aorta above the cardiac shadow as observed in the left anterior oblique views.

The right border of the vascular pedicle is formed by the superior vena cava in the majority of young subjects, in later life it is more frequently formed by the right border of the ascending aorta. An increase in the transverse diameter of the vascular pedicle in the frontal roentgenogram does not specifically indicate enlargement of the aorta, for this may result from tortuosity alone, however, this measurement is useful in that it does distinguish between a normal and abnormal aorta. In a recent study, it was found that the transverse aortic diameter in normal subjects is closely related to weight and height¹⁸. The table established for predicting the transverse diameter of the heart from weight and height may be employed equally well for the aortic arch diameter. A correction for age is necessary, 1 mm is added for each three years over the age of 43, and subtracted for each three years under the age of 43. Deviations from the predicted value up to ten per cent are within allowable normal limits, but deviations in excess of this are infrequently seen, and the aorta may be considered as almost certainly abnormal if the diameter exceeds 15 per cent above the predicted value, for 92 per cent of normal subjects fall within this range. The transverse diameter of the aortic arch is a simple and valuable standard for measurement of the aorta. It is important that the roentgenogram be made with the subject properly centered for even slight rotation into the oblique positions markedly alters the aortic arch transverse diameter. If the diameter is found to exceed normal values, further study in the left anterior oblique position is indicated for the aortic arch is best visualized in this view.

On the same nomogram chart employed for determining cardiac areas, we have, in the lower section included a nomogram for the predicted transverse diameter of the aortic arch and transverse diameter of the heart, based on our table. This nomogram chart, therefore, serves as a simple method for the application of all the measurements necessary, i.e., the transverse diameter of the heart, the frontal cardiac area, and the aortic arch transverse diameter.

We have devoted the greater part of this presentation to a discus-

sion of cardiac measurements and to certain phases of cardiac enlargement which have interested us, such as electrocardiographic changes, the lead scale method to replace orthodiascopy, obliteration of the infra-bronchial space as a sign of left atrial enlargement, the arc method of determining the diameter of the aorta, and tables and nomograms for transverse diameter and frontal area. I do not wish to leave you with the impression, however, that the recognition of enlargement is the only important consideration in roentgenologic study of the heart. Time does not permit us to go into detail, but we have already briefly indicated that fluoroscopic study of the individual heart chambers is an invaluable aid in various types of heart disease. Observation of the cardiac pulsations also contributes such information, particularly in cardiac infarction, constrictive pericarditis and pericardial effusion. The cardiac pulsations may be analyzed objectively by means of roentgenkymography, a technique which has proven of value not only in clinical problems but in physiological studies as well, such as determination of cardiac output.⁷ One of the really significant advances in cardiac roentgenology in the past few years has been the technique of contrast visualization of the cardiac chambers with diodrast, introduced by Robb and Steinberg.¹⁰ The application of the method has been advanced notably with the multiple exposure method,²⁰ and has proven of particular value in the diagnosis of congenital cardiac lesions.²¹

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WILLIAM WORTHINGTON HERRICK
1879-1945

IN MEMORIAM

WILLIAM WORTHINGTON HERRICK

DR HERRICK was, above all else, what Sir William Osler would have called a true physician, a doctor's doctor, the one chosen by his confreres as their consultant. Those of us who are left bereft by the suddenness of his passing are sustained by the thought that he had attained the highest honor his friends could give him—The Presidency of The New York Academy of Medicine.

William Worthington Herrick was born in a country parsonage in Sherman, Connecticut. His father was pastor of the church for sixteen years. Six of his great uncles had been doctors and when he was fifteen he made up his mind to be a physician. Three generations of Herricks had preceded him to Yale. Upon his office wall hang the Yale diplomas of his great-grandfather (1798), his grandfather (1822), his father (1871), his own (1902), and that of his son (1933). After graduating from the Yale Medical School with high honors in 1905, he spent the next two years as an interne at St. Luke's Hospital in New York where he worked in both the pathological and medical services.

At some time during these years of internship, he developed tuberculosis. It was a challenge to his medical science. He returned to the family home in Gaylordsville, Connecticut, and, as he often told the story, "rested on a cot out of doors and drank milk until he was cured." For a time after his recovery, he assisted the local doctor and thus got his first taste of private practice.

For the next four years Dr. Herrick was assistant to Drs. E. G. and Theodore Janeway in New York. At this time the teaching of medical students became of intense interest to him and from 1908 on he served successively as Instructor, Assistant, Associate, and then full Professor of Clinical Medicine at the College of Physicians and Surgeons of

Columbia University From 1910 to 1929 he was Assistant Attending Physician at Roosevelt Hospital

During World War I, Dr Herrick served as a Major in the United States Army and was Chief of Medical Service at Base Hospital, Camp Jackson, S C Toward the end of the war he was medical consultant for the Southeastern Department

During the present war he was a member of the Medical Advisory Board of Selective Service System of New York City and Chairman of the Physicians and Surgeons group of the American Red Cross War Fund for 1945

His medical writings date from 1908 and scarcely a year passed without the publication of a carefully written paper upon the subject he was studying at the time He was especially interested in the metabolic disorders, meningococcus meningitis, trichinosis, complications and toxemias of pregnancy, and later, in diseases of the heart and lungs About 1924 he assumed the complete editorship of the Nelson Loose-Leaf Medicine and until his death was responsible for these many volumes

In all his fields of endeavor, he gave evidence of his ability both as an organizer and executive He drove himself hard He expected nothing of his associates which he would not do himself In his private practice, the younger men who have worked with him got invaluable training and experience by constant association with his expert wisdom and thoroughness, and then with his encouragement they branched out upon their own To these younger doctors he was a rock upon which they leaned

He said of himself that he had a single track mind—his objective being to further the cause of medicine through the training of the next generation of physicians

To his patients he was a hope and a consolation Each one who came to his office for diagnosis was a challenge to him With infinite patience he would try to reach the correct solution of these complicated medical problems That one of his special interests was in diagnosis was shown in his teaching and in a scholarly paper presented before the Practitioners Society on "A Consideration of Diagnosis including its Logistics"

Individual and social medical problems to him were never static His address on assuming the Presidency of the Academy was entitled

Scientific humanism in this changing world

At the time of his death not only was he carrying the responsibilities of his private practice and The Academy of Medicine, he was attending physician at Presbyterian Hospital, vice president of Trudeau Sanatorium and Internist on the Medical Staff of the New York Central Railroad

He was a member of the Board of Trustees of Sharon Hospital, Sharon, Connecticut and on the consulting staff there. He visualized the need for an enlarged and modernized hospital which would serve Sharon and the surrounding communities and he was working toward this accomplishment.

Dr. Herrick was a man of many resources. He was an inveterate reader, he enjoyed music and for relaxation played the pipe organ and the piano. During the summer he spent many hours in the work-shop of his Connecticut home, doing wood-carving and making reproductions of old furniture. He enjoyed long walks in the woods, he fished and played golf. His farm was a constant source of interest to him. He often said that everyone should have a piece of land to call his very own.

He died, as he would have wished to go, suddenly, without warning, at the height of his powers. He has left us the memory and example of a great man, admired, respected and loved not only for his professional attainments, but for his intellectual honesty and his personal integrity.

JOSEPHINE HEMINGWAY KENYON

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OCTOBER 1945

DECOMPRESSION SICKNESS AND BUBBLE
FORMATION IN BLOOD AND TISSUES*

Harvey Lecture, October 26, 1944

E NEWTON HARVEY

Henry Fairfield Osborn Professor of Biology
Princeton University

INTRODUCTION

AFTER the last World War, 1914—1918, an editorial in the *Journal of the American Medical Association*, in referring to medical aspects of aviation and praising the work that had been done to protect aviators against the effects of altitude, spoke of the necessity of speed and the ability to climb above an opponent. At that time bombing and observation planes flew "for hours at altitudes of 12,000 to 15,000 feet" while pursuit planes attained "the enormous altitude of 18,000 and 20,000 feet".¹ In the second World War a service ceiling of well over 40,000 feet has been attained, a height where even the breathing of pure oxygen is not sufficient to supply the needs of the body. Without the protection of a pressurized cabin, man has become the limiting factor to high ascent.

* The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Princeton University.

But considerably below 40,000 feet, a series of symptoms have been described which cannot be attributed to any one of the three common and obvious difficulties at great height (1) lack of oxygen, (2) ear and sinus trouble, due to non-equalization of pressure between middle ear (or sinuses) and the external atmosphere, (3) intestinal pains, due to the expansion of gas in the digestive tract. A fourth group of additional symptoms may appear and affect various parts of the body. These range from a mild rash or ache to unbearable pain near the joints, from tightness in the chest to serious coughing spells and from hyperesthesias or anesthetics to convulsions, paralysis and syncope. The individual is definitely incapacitated, sometimes seriously. Since the symptoms may begin to appear as low as 25,000 feet and are marked at 35,000 feet, they limit the altitude at which an open plane can be flown, for these heights are well below the point (38,000 ft) at which pure oxygen just begins to fail in supplying the retina and brain. Any of the above group of symptoms, fully described in Armstrong's² classic book on Aviation Medicine, constitute decompression sickness* since they result from decompressing the body from one atmosphere to lower values, an analogous change to the return of a person to one atmosphere after a previous exposure to compressed air. Decompression sickness may also be applied to the symptoms resulting from the latter change, although the older terms, compressed air illness or caisson or diver's disease, have been more frequently used.

In both compression-decompression experiments and in low pressure or "altitude" experiments, excess gas is dissolved in the body. The tissues are saturated at a certain gas pressure, producing a similar tension of dissolved gas in the cells and tissues, and then the gas pressure is decreased. The procedure can be compared to removing the cap from a soda water bottle or exhausting a tube of water with an air pump. Under certain conditions bubbles will form in both cases. It has long been recognized and appears quite certain that compressed air illness is due to bubble formation in blood and tissues. By analogy the symptoms at high altitude might also be expected to result from bubbles, although the question, until recently, had by no means been settled and other theories had been proposed. Indeed, the formation of bubbles in animals at low barometric pressures had been

* Armstrong has suggested the word *aeroembolism*, but this term implies unproven ideas about the origin of the symptoms.

denied by the father of barometric studies, Paul Bert

Early in the organization of the Committee on Medical Research, the division of Aviation Medicine foresaw the seriousness of decompression symptoms and established the Subcommittee on Decompression Sickness, with John F. Fulton, of Yale University, as able Chairman. The present basic study was undertaken in order to separate and analyze the fundamental factors involved in the formation of bubbles, with special reference to the conditions found in animals, and with the purpose of applying the findings to the aviator. Critical terminal experiments can be carried out with animals that cannot be undertaken with man. Moreover, the whole problem of bubble formation in liquids was in a little known state at the time this work was started in May, 1942.

Many other groups of investigators have been sponsored by this Subcommittee. It is not possible, for security reasons, to refer to the vast amount of detailed data collected by these groups. The reader is referred to reports that will eventually be published, prepared under the direction of the responsible investigators—Behnke, Bronk, Blankenhorn and Ferris, Evans, Fulton, Greeley, Harvey, Hitchcock, Ivy, Jacobs, Knisley, Lawrence and Hamilton, Scott, Swindle, Whitaker, Blinks and Twitty—as well as the many Army and Navy experimental and training stations in this country, in Canada and in England.

It is a pleasure to express here my sincere appreciation of the keen interest, fertile ideas and extended experimentation of the men who have collaborated on the Princeton project.* Wm. D. McElroy and Mr. A. H. Whiteley, members for the full period of the contract, and D. C. Pease, G. H. Warren, K. W. Cooper and Wm. Kleinberg, part of whose time has been devoted to the work. I am also particularly grateful to Professor Henry Eyring, of the Chemistry Department, Princeton University, for much helpful discussion, and especially to Mr. D. K. Barnes, who has worked out a detailed theory of the separation of a gas phase from a liquid and clarified our knowledge of the conditions for stability and growth of gas masses.

HISTORY

Probably the first bubble recorded in animals was that seen by

Robert Boyle³ in the eye of a snake which he had placed under his newly invented air pump in 1670 Boyle's remarks are so pertinent to our subject and so prophetic of what has now been realized in aviation that I quote him in full After describing an experiment with fresh blood and another with fresh milk which boiled vigorously on evacuation with his pneumatical engine, he says

Note, that the two foregoing Experiments were made with an Eye cast upon the inquiry, that I thought might be made, Whether, and how far the destructive operation of our Engin upon the included Animal, might be imputed to this, that upon the withdrawing of the Air, besides the removal of what the Airs presence contributes to life, little Bubbles generated upon the absence of the Air in the Blood, juices, and soft parts of the Body, may by their Vast number, and their conspiring distension, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones, that convey the Blood and Nourishment, and so by choaking up some passages, and vitiating the figure of others, disturb or hinder the due circulation of the Blood? Not to mention the pains that such distensions may cause in some Nerves, and membranous parts, which by irritating some of them into convulsions may hasten the death of Animals, and destroy them sooner by occasion of that irritation, than they would be destroyed by the bare absence or loss of what the Air is necessary to supply them with And to shew, how this production of Bubbles reaches even to very minute parts of the Body, I shall add on this occasion (hoping that I have not prevented my self on any other) what may seem somewhat strange, what I once observed in a *Viper*, furiously tortured in our Exhausted Receiver, namely, that it had manifestly a conspicuous Bubble moving to and fro in the waterish humour of one of its Eyes

Although sporadic observations were made after Boyle, real knowledge of the effects of varying atmospheric pressures began with Paul Bert's systematic study, published as *La pression barométrique* in 1878⁴ Bert demonstrated the presence of bubbles in the blood and tissues of animals after compressed air experiments but denied the existence of such bubbles in animals exposed to low pressures, although Hoppe⁵ in 1857 had previously reported bubbles to be present in animals at 50 mm Hg (62,000 ft) To further study the problem, Hill and Greenwood⁶ in 1910 exposed eight mice, two guinea pigs, a kitten and a rabbit to 50 mm Hg air pressure until the animals died and then examined them post-mortem No bubbles were found in any except the rabbit whose heart and large vessels were full of air They concluded that in general Paul Bert was right Actually, both Hoppe and Bert were correct for we now know that resting animals at high altitudes rarely develop bubbles but if they are exercised with vigorous muscle contraction, bubbles appear in the blood quite regularly These conflicting results, as well as the doubts expressed by various workers that bubbles appear in blood at altitudes, must be attributed to the chance variation in amount of movement tak-

ing place in the animals under experimentation

The bad effects of deep diving have long been known but the problem of illness after exposure to high air pressures became particularly important with the invention in 1840 of the caisson, a compressed air chamber for sinking shafts or tunnels or for building piers under water. With the extended use of this device and the compressed air diving suit in the latter part of the last century, diver's or caisson disease became common. A series of words were coined by the workers to describe the symptoms. Among these the "bends," the "chokes" (or "chokers"), the "itch" and the "staggers" are the most picturesque and describe quite adequately joint pains, respiratory difficulties, skin eruptions and paralyses. The experience from actual flying and in high altitude chambers indicates that all the above symptoms may also occur. Skin trouble and nervous affections are rather rare but the bends and chokes are frequent and these words have become a permanent part of the scientific vocabulary of the subject.

Interest of the British Admiralty in diving led J. S. Haldane⁷ with Boycott and Damant^{8,9} as well as Leonard Hill¹⁰ to their extensive research in 1906 to 1908 while in the United States beginning in 1935 Behnke^{11,12} and associates, Shaw, Willmon and Yarbrough and Shilling,^{12a} have extended our knowledge, making special studies of nitrogen elimination, fat content and the use of helium for unusually deep diving to eliminate the dangers of oxygen poisoning and nitrogen narcosis. In Germany the classic contribution of Heller, Mager and von Schrotter¹³ compiles the facts on diving up to 1900.

The symptoms of caisson disease could be immediately alleviated and a life often saved by recompressing the patient and then decompressing more slowly, allowing time for excess gas to be removed from the body. Chambers for this purpose were first introduced by Sir Ernest Moir about 1890. The increased pressure contracts the bubbles and this fact proves that symptoms only appear when bubbles reach a certain size. Experience at simulated high altitudes likewise indicates that recompression to lower altitudes (even a change from 35,000 to 25,000 feet) will also instantly relieve bends and chokes but upon immediate reascent the pain will reappear in exactly the same place.

Such facts lead to the inescapable conclusion that decompression sickness results from the formation of gas bubbles in the body and

multiplicity of symptoms reflects the region in which the bubbles grow or lodge. The relief or treatment of decompression sickness is an accomplished procedure—immediate recompression. Prophylaxis remains to be considered. If bubble formation could be prevented in the body when its tissues are supersaturated, bends would cease to be a problem.

It is obvious that a fundamental study of the conditions under which gas will separate from solution is absolutely essential. In addition the composition of the gas which forms the bubbles must be known and every possible fact that might bear on the problem. Consequently, a study of bubble formation has been undertaken under the simplest conditions easily attainable, in water saturated with a single gas in a glass vessel. This study has been supplemented by investigations of blood *in vitro* and also in the body of narcotized animals, for it is in this fluid, i.e., in the blood vessels, that bubbles most frequently occur. The condition may be called pompholyhemia and we have used this symptom in our study of the cat as an index to evaluate similar procedures which might cause or prevent decompression sickness in man.

BUBBLE FORMATION FROM EXCESS GAS

Many important principles can be demonstrated with a bottle of soda water in which carbon dioxide is dissolved at a tension of 3 or 4 atmospheres. If the chilled bottle has remained upright and undisturbed for some time, no bubble will form when the cap is removed but on tipping the bottle so that soda water flows over the dry glass surface bubbles immediately appear, and on carefully pouring into a dry tumbler abundant bubbles cling to the walls. There may frequently be observed a chain of bubbles arising from a point where a gas mass remains sticking to the glass. Sometimes bubbles also arise from a clearly visible dust particle in the bulk of the liquid. If the tumbler is greasy, the hydrophobic region will be outlined by abundant bubbles which persist until the soda water has lost its excess gas. In fact this "bubble test" will tell how thoroughly a tumbler has been washed.

The bubbling and effervescence is all due to minute gas masses which stick to the dry walls or to dust particles and grow into bubbles as soon as the pressure release occurs. We can prove this

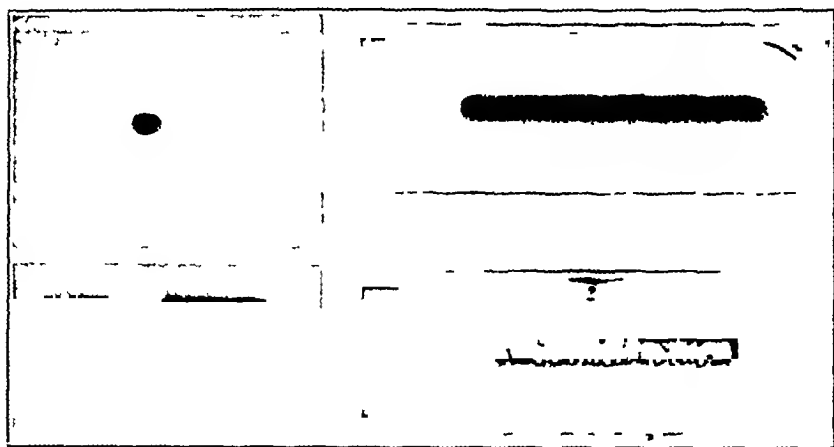


Fig 1

Fig 2

Fig 1 (left) Photograph of an air bubble under a glass (above) and a paraffin surface (below)

Fig 2 (right) Photograph of an air bubble in a glass capillary (above) and a hydrophobic capillary (below) In the latter the concave curvature of the air surface cannot be seen but it is indicated by the fact that the transmitted white band of light does not reach the edge of the gas cylinder The air bubble on glass is 1.65 mm across

by gently pouring the soda water into a scrupulously *clean* and *wet* tumbler, when no bubbles form, except during the first disturbance of the surface due to pouring. If some dry powder, such as infusorial earth, is now dropped into the quiet soda water the carbon dioxide separates with explosive violence but if the infusorial earth has been first boiled in water to remove its air films and then placed while wet into the soda water, not a single bubble will appear. However, a paraffined surface (hydrophobic), no matter how well cleaned, will always bubble profusely.

GAS NUCLEI

These effects are all due to small gas masses, or gas nuclei, which stick to any dirty, especially greasy, surface but not to clean wet glass. The sticking of gas is a matter of contact angles, which are well seen from the form of bubbles in capillary tubes or on surfaces. As shown in Figure 2, a bubble in a glass capillary filled with water has rounded (convex) ends—the contact angle (measured through the water) is zero, in a paraffined capillary the gas bubble has concave ends and

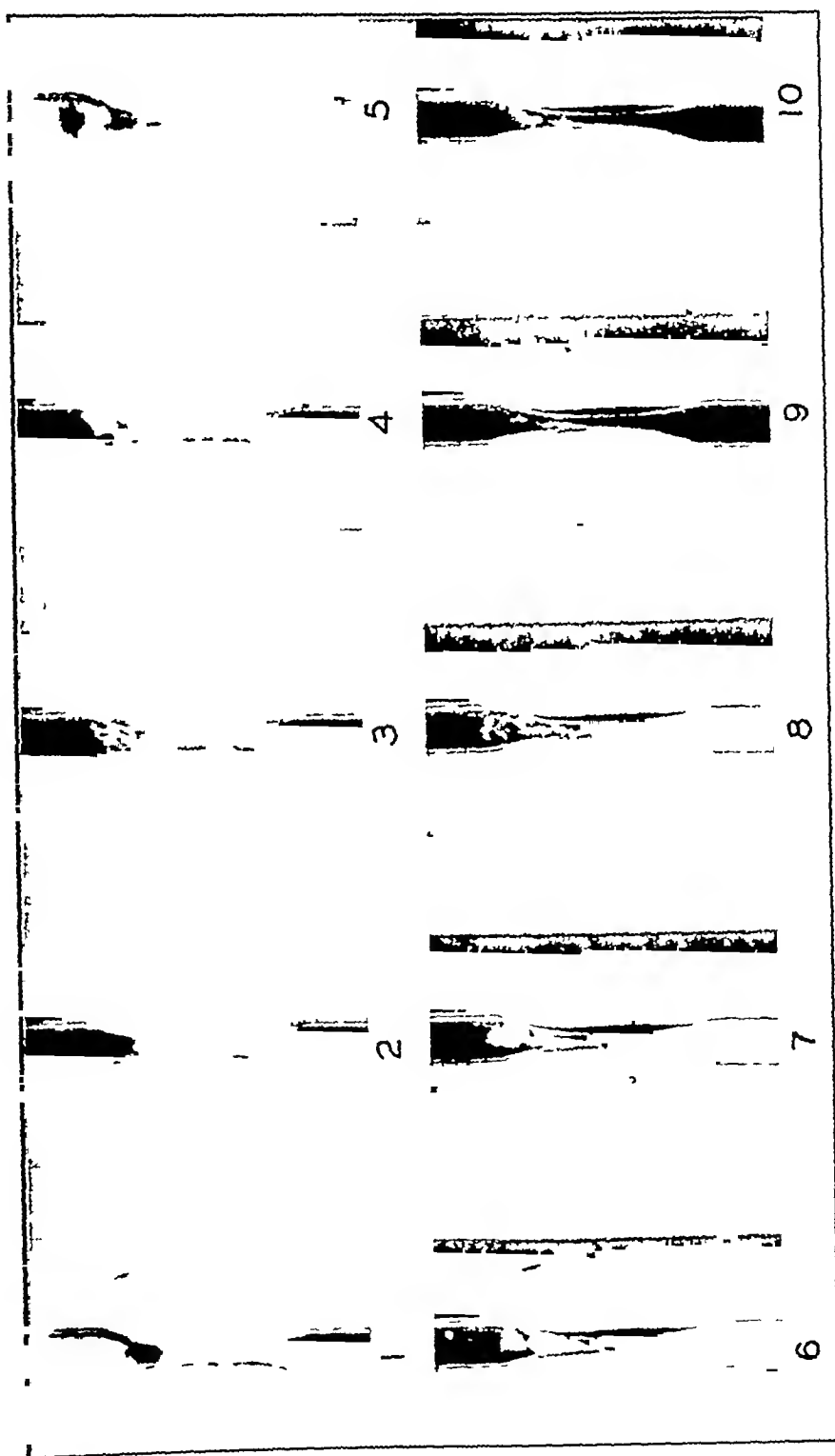


Fig. 3 Negative prints from a high-speed movie (1,680 frames per second) of cavitation in a Reynolds' tube of 10 mm diameter. Flow from bottom to top. Note the periodic cavitation (white in appearance) beginning at a particular spot on the narrow region of the tube. The individual frames are numbered

the contact angle is about 108° . Since the form of gas bubbles in blood vessels is similar to that of water in a glass tube, we may conclude that the endothelium is, on the average, hydrophilic, an important fact for the theory of bubble formation.

On a plane surface the form of bubbles is illustrated in Figure 1 and the contact angles are clearly visible. On a completely hydrophobic surface like glass, the zero contact angle means that no bubble can stick and no nucleus can remain but with any positive contact angle nuclei can stick and may be stable under certain conditions.

BUBBLE FORMATION FROM NEGATIVE PRESSURE

The development of bubbles in a liquid saturated with gas at one atmosphere and under one atmosphere pressure is uncommon but a number of examples are known. Such bubble formation is due to local decrease in hydrostatic pressure. A most interesting case was described by Osborne Reynolds¹⁴ at a constriction in a pipe. When water flows through a tube which is narrowed at one place, the velocity is obviously increased at the constriction and, by Bernoulli's law, the pressure must decrease. In addition, violent turbulence and vortices appear.* If the constriction is narrow enough and the velocity sufficient, very low pressures will be produced and the water will suddenly break into cavities (cavitation) with a hissing sound. When the cavities collapse, which they do periodically, as shown in Figure 3, bubbles of gas remain and can be seen in the water leaving the constriction. Reynolds called the phenomenon "the boiling of water in an open tube at ordinary temperature." Whenever a local constriction occurs in a blood vessel, whether from a spasm or from passive squeezing between muscles, the pressure must be lowered at the constricted point, but it is doubtful if the velocity of flow is sufficient to produce Reynolds' cavitation in the body.

Another example is the cavitation which appears in water due to the passage of intense sound waves, or the bubbles which will form in a test tube of water at one atmosphere pressure if the bottom is hit a series of blows. Just as sound waves are made up of pressure changes, with increased followed by decreased components, so the series of blows involve increased followed by decreased pressure. A blow (or even vibration) to the human body at altitude would

* Dean^{11a} believes most bubble formation in water free of gas nuclei is due to vortices.

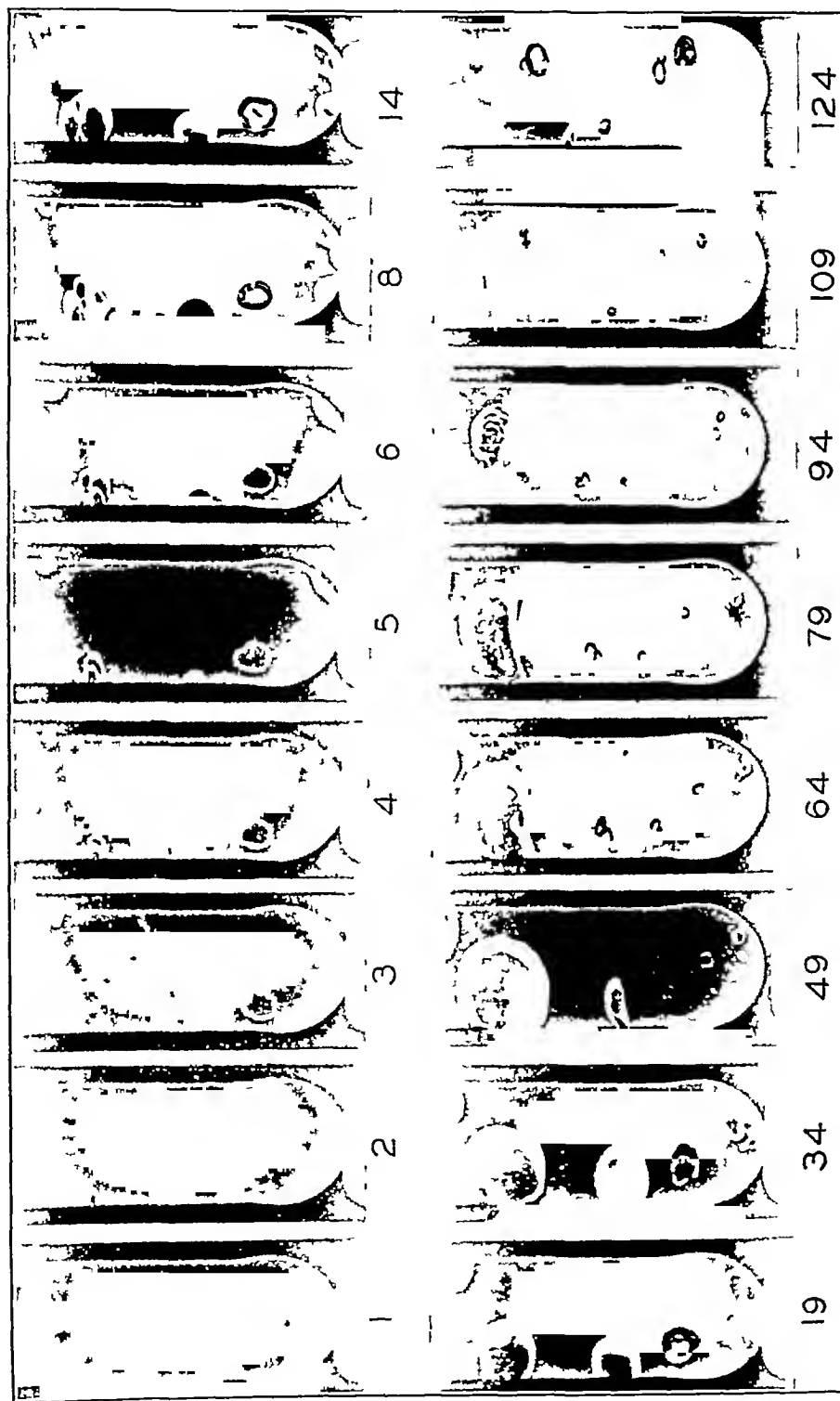


Fig. 4. Negative prints from a high-speed movie (1,200 frames per second) film of cavity formation in a glass tube (19.3 mm diam.) filled with air saturated water but under a low pressure, when the bottom is struck a blow. The initial cavity oscillates in volume several times before the final bubbles start rising to the surface. The individual frames are numbered.

tend to bubble formation, but might not necessarily actually produce bubbles unless intense

Whenever tensions are built up, as when a glass rod immersed in water is suddenly withdrawn, or when a propeller blade by rotation continually pulls away from the water, cavities may be formed and bubbles appear

If the liquid, already supersaturated with gas, is subjected to a blow or any other treatment described above, the formation of bubbles is greatly facilitated. The results of cavitation become particularly important at high altitudes where the pressure is already near the vapor pressure of water, much less in compression-decompression experiments where the final pressure is one atmosphere, far from the vapor pressure of water. A series of photographs of cavity and bubble formation in a tube of water at 110 mm Hg pressure (the equivalent of 45,000 feet) after striking the bottom with a wooden block is reproduced in Figure 4

The tensile strength of water is believed to be very high. This is demonstrated by experiments in which a slow steady pull is applied, as in those of Berthelot¹⁵ and of Dixon,¹⁶ where clean degassed glass tubes were completely filled with water at a high temperature and the temperature then lowered, allowing the greater differential volume contraction of water as compared to the glass vessel to develop the pull. Negative pressures (tensions) as high as 150 atmospheres were found before the liquid suddenly broke, leaving a cavity.

This experiment is quite comparable to taking a piece of paper by two opposite edges and trying directly to pull it into two halves. The necessary effort is very great. On the other hand, by grasping one edge of a piece of paper with the two hands and twisting in opposite directions, the paper can be torn in two with the greatest of ease. The same amount of energy is required in either of the two methods but the rate of application of the energy (the power) necessary by the first is enormous, by the second very small.

Since tension is the negative equivalent of pressure* (i.e., negative force per unit area), if the area is small, enormous tensions may develop. In a liquid pressures or tensions quickly become equally distributed, as illustrated by Pascal's law, but, if the tension develops

* Pressure in a gas can never become negative but in a liquid, gel or solid high negative pressures develop if the material is subject to a pull.

in a very short time interval, inertia and viscosity of the liquid may result in local high tensions (perhaps 100—1,000 atmospheres) so that the liquid is literally torn apart

Considerable space has been devoted to this conception since we deal in the animal body with surfaces that *can* be *torn* apart and local pulls are involved rather than the uniform conditions of the Berthelot and Dixon experiments. Working with presumably gas nucleus free apparatus we can sometimes experimentally demonstrate the formation of cavities on the end of a glass rod drawn out of water in a narrow tube when the velocity reaches about 16 meters per sec. With corn syrup the velocity can be very low because of the inability of the viscid liquid to move into the space left by the rod, and with gelatin gel only a slight movement is sufficient to form a cavity. Moreover, the weight necessary to pull a glass rod out of gelatin is only a few kilograms and the local regions of high tension can be seen as strain patterns when viewed between crossed polaroids. Gas always moves into these cavities with extraordinary rapidity and a bubble is left when the cavities collapse.

That such a mechanism must be involved in the formation of bubbles in the animal can be demonstrated in excised tissues manipulated by pulling and cutting under conditions properly controlled to insure that extraneous gas nuclei are not introduced. Connective tissue is particularly prone to form bubbles by this procedure and it is perhaps significant that the bends are associated with regions rich in connective tissue.

THE PRESSURE DIFFERENCE, ΔP

From the preceding discussion it is apparent that the tendency for bubbles to form will depend on two factors, both on gas dissolved and also on pressure in the liquid. The difference between these may be called the pressure difference, ΔP . It is numerically equal to the gas tension, t , minus the hydrostatic pressure, P . The gas tension is determined by Henry's law, which states that at equilibrium the tension of gas dissolved in a liquid is proportional to the partial pressure, p , of gas, which may be measured in atmospheres, in contact with the liquid. The hydrostatic pressure can be either positive or negative and may also be measured in atmospheres. The pressure difference, $\Delta P = t - P$, is one of the primary reasons for bubble

formation in compression-decompression and in low pressure experiments

If a gas nucleus is present, any change in ΔP will change its volume. However, if gas nuclei are absent, the question arises as to how great ΔP must be before bubbles will form spontaneously, i.e., how much supersaturation is possible before gas bubbles appear *de novo* in a homogenous liquid at rest. A treatment based on thermodynamics and statistical mechanics indicates 100 to 1,000 atmospheres for spontaneous bubble formation. This is confirmed experimentally by Kenrick, Wismer and Wyatt,¹⁷ who have demonstrated that water, if undisturbed, may be brought into equilibrium with at least 150 atmospheres of gas without forming bubbles when the pressure is released.

This statement regarding high ΔP for spontaneous bubble formation applies also to water in contact with hydrophilic surfaces whether smooth or rough and to hydrophobic surfaces if molecularly smooth but, if pitted or containing cracks, gas nuclei can form *de novo* and grow to bubbles at less than 100–1,000 atmospheres gas tension. Theoretically, if a crack or a cone shaped cavity exists with a sufficiently small angle, *de novo nucleus formation* should occur without supersaturation with gas. This *de novo nucleus* may then grow to a bubble under the conditions which control the growth of any other nucleus.

THE EFFECT OF DIFFERENT GASES—DIFFUSION

When compared at the same tension different gases will behave alike except when rates of diffusion are important. In this case not only ΔP but diffusion constants and especially solubility must be considered. A highly soluble gas like carbon dioxide, even at a low tension, may play an important role in the early growth of a bubble by diffusion because of the high concentration of carbon dioxide molecules.

The effect is well seen when a vapor cavity is produced in a liquid by negative hydrostatic pressure. If both carbon dioxide and nitrogen are dissolved at the same tension in the liquid surrounding the cavity, they will diffuse into the cavity at rates depending on their concentrations (since the diffusion constants are nearly alike) rather than their tensions. When the vapor cavity collapses there will be a much greater proportion of carbon dioxide than of nitrogen in the bubble that persists. Later the proportion of carbon dioxide and nitro-

gen will adjust, so that at equilibrium an equal amount is present, i.e., a proportion that reflects their partial pressures

Likewise, the size of bubbles will be greater if carbon dioxide rather than nitrogen is diffusing into them, both from the same tension. The rapid exit and entrance of carbon dioxide into bubbles is easily demonstrated by filling a long glass tube with layers of water alternately saturated with air and with carbon dioxide. The carbon dioxide layer may be colored with a dilute dye to render its boundaries visible. If minute bubbles are now produced in the air-saturated layer at bottom by striking the slightly evacuated tube a blow, the bubbles rise slowly, but when they pass into the carbon dioxide layer they jump in size, due to more rapid diffusion of carbon dioxide inward than of air out, and rise rapidly until they reach the air-saturated layer. Then carbon dioxide passes out of them rapidly, they suddenly shrink and rise slowly until the next carbon dioxide layer is encountered, when the process is repeated. We may imagine a rapid bubble growth in contracting muscle when carbon dioxide is produced, followed by the later replacement of this gas with nitrogen for permanent bubble formation.

STABILITY AND GROWTH OF GAS NUCLEI

Gas supersaturation is like salt supersaturation, with this exception. The presence of a minute crystal of the salt is sufficient to start crystallization of the whole salt solution, whereas a gas nucleus may enlarge to a certain point in a gas supersaturated liquid but will not grow indefinitely until certain critical conditions are surpassed. The conditions are simple and clear in a sphere. The surface tension of the gas-water interface exerts an inward pressure which is inversely proportional to the radius and amounts to an extra atmosphere in a bubble in pure water of 3μ radius. This excess pressure forces the gas into solution and the bubble disappears. Small spherical bubbles cannot exist unless there is excess gas in the liquid and the conditions for stability are that $\Delta P = 2\gamma/r$, when γ is the surface tension and r the radius of the bubble.

For a gas mass sticking to a surface the conditions of stability are much complicated, since the configuration of the surface and the gas mass which may have two radii of curvature at right angles to each other, as well as the receding contact angle, which determines

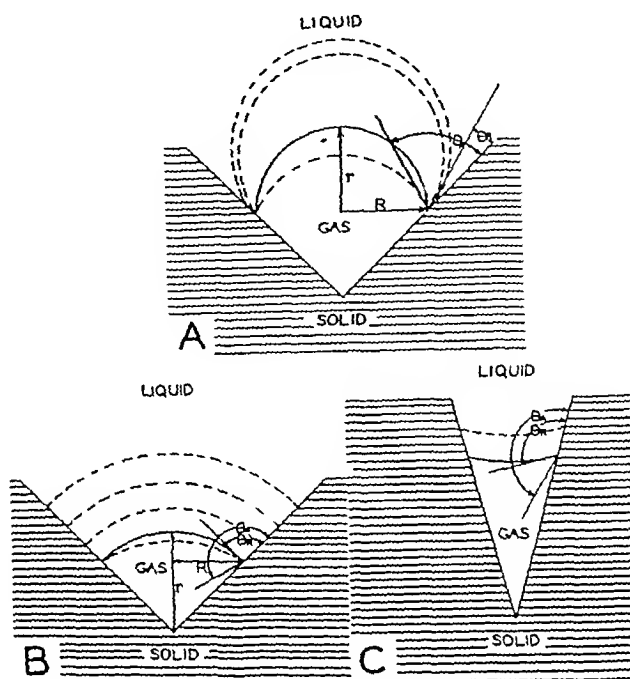


Fig 5 A A gas nucleus in a conical cavity of apical angle Ψ , and small receding contact angle, θ_R θ_A , advancing contact angle. R , radius of base, r , radius of curvature of gas-water interface at moment of instability (solid line) The dotted lines show stages of growth The hemisphere limits stability B A similar gas nucleus in a conical cavity with large receding contact angle which limits stability C A gas nucleus in a cone of acute apical angle, Ψ , so that $\theta_R > 90^\circ + \Psi/2$ Note curvature of gas-water surface.

“creep” of the gas nucleus, are all important. It is not possible to describe in detail the conditions for stability of gas nuclei on surfaces but Figure 5 illustrates what will happen in cases which have been considered in a recent paper by Harvey et al.¹⁸

Wherever a surface is concave to the gas phase, as in Figure 5, C, the pressure in the gas is less than the gas tension in the water and gas would tend to move in from solution thereby continually enlarging the gas mass.

For every gas nucleus there is a certain ΔP below which it is stable and above which it grows by diffusion of gas. We may look upon a test tube of water, not especially cleaned to remove gas nuclei, as containing a population of gas nuclei of varying dimensions, each one of which will grow at a certain critical ΔP . If exhausted to one-half atmosphere, a group of bubbles will arise and then

no more appear, but on reducing the pressure to one-quarter atmosphere another group of bubbles arises. This formation then ceases but at one-eighth atmosphere another group arises and so forth. At the vapor pressure, a ΔP of $760 - 20 = 740$ mm Hg, the hydrostatic pressure, P , has been reduced as much as possible by evacuation but by striking the tube, a pressure pulse with a tension component is set up and P becomes less than the vapor pressure, giving rise to growth of a new series of gas nuclei with the formation of more bubbles. For convenience we can call all nuclei which will grow at or above the vapor pressure of water, gas macronuclei, while those which require a greater ΔP for continued growth are gas micronuclei. The distinction is quite arbitrary and merely represents a convenient line of demarcation.

REMOVAL OF GAS NUCLEI

For any experimental work with animals it is necessary to use liquids in containers or implements which have no gas nuclei sticking to them, otherwise quite erroneous conclusions may be drawn regarding the bubbling of blood, spinal fluid or tissues. Any bubbles which appear in such an experiment may have come from gas nuclei on the surgical instrument or apparatus rather than from the blood or tissue (see Harvey et al.¹⁰)

The first necessity for avoidance of gas nuclei is to avoid hydrophobic material. This is not because a hydrophobic surface cannot be cleaned of gas nuclei, for it can, if always under water, but because the water runs off when exposed to air, and an air film then sticks by virtue of its contact angle. The surface should be so clean that a water film will cover it *completely* when removed to the air. If container and water are then well centrifuged, macronuclei or dust particles on glass can be removed and the water will not bubble at the vapor pressure. After treatment by this method, M HCl and M NaHCO₃ can be mixed without bubble formation and yeast can be grown in gas-nucleus-free culture medium with copious carbon dioxide production but without formation of bubbles. Filtering may also be employed to remove gas nuclei but it is essential to make certain that no gas masses are present on the filter, for filtering sometimes introduces more nuclei than it removes.

For removal of gas micronuclei two additional methods are avail-

able, both highly effective. One removes gas from solution by prolonged boiling or evacuation, thereby allowing the nucleus to disappear by solution in gas-free liquid, the other makes use of increased hydrostatic pressure, thereby forcing the nucleus into solution. The latter method is the most convenient, since the liquid retains its previous gas tension after a high pressure treatment and the difficult task of resaturation without introducing gas nuclei is avoided. We have placed both water and container in a steel chamber filled with water, and have used a hydrostatic pressure of 16,000 lb/in² (1,090 atmospheres) for 15 to 30 minutes. Such previously compressed water in a clean glass tube has remarkable properties. It can be heated to at least 202° C before bursting into vapor, although evaporation from the surface is enormous. When intense high frequency sound waves are passed through, no cavitation occurs and no bubbles arise. Finally, if exhausted to the vapor pressure of water at 20° C, moderate knocks have no effect and only a very severe blow, strong enough nearly to shatter the glass, will cause bubbles to form.

Although this water is gas-nucleus-free, bubbles can still be produced in it by procedures which increase ΔP to the 100 to 1,000 atmospheres necessary for spontaneous bubble formation—either by decreasing P , as when a glass rod is rapidly pulled out of the water with cavitation and bubble formation, or by increasing t , as when such water is electrolyzed and the gas concentration rapidly rises at the electrodes or when frozen and the formation of ice crystals (in which gas is insoluble) raises the gas concentration to a high value in pockets of the unfrozen liquid.

GAS NUCLEI IN BLOOD

With these fundamental principles in mind we may now turn to the animal and apply them to the observed facts. At altitude bubbles are rarely observed in resting animals but do appear in blood vessels as a result of muscle contraction, whereas in resting animals decompressed to one atmosphere from high air pressures the bubble formation is profuse in blood vessels, and many tissues are a froth of bubbles.

Since bubbles appear most readily in blood it was natural to test this liquid for gas nuclei. Previous experience with glass models and methods of removing gas nuclei have supplied the technique for drawing samples of blood into a long clean wet glass tube, or pompholy-

gometer, one end of which is a cannula inserted and tied in the blood vessel. By appropriate clamps, stop-cocks and connections to a vacuum reservoir, successive samples of blood in the pompholygometer can be tested below the blood vapor pressure at 38°C to see if gas nuclei are present which will grow into visible bubbles. The testing conditions of less than 47 mm Hg are equivalent to an altitude of 63,000 feet (a ΔP of 713 mm), far greater than the animal itself can stand.

The carotid blood when sampled in the above manner has been found to be free of gas nuclei in resting cats at ground level as well as in cats after a previous exposure to high altitude*. Even when the blood is drawn at an altitude of 45,000 feet or during a prolonged exposure to an air pressure of 100 lb/in², bubbles have not appeared at the vapor pressure except in a few instances where contamination was suspected. These experiments indicate that all the formed elements of the blood (red and white corpuscles, platelets, fat globules or blood dust) play no part in bubble formation, that air masses do not normally pass from alveoli to lung capillaries (although they may when the alveolar air pressure is raised above that in the capillaries) and that movement of the blood with turbulence and vortex formation around the valves of the heart does not normally start bubble formation. They lead to the conclusion that bubbles must arise from gas nuclei sticking to or formed on or within the endothelial linings of the vascular system or extravascular spaces and only when they have enlarged to the point of instability do they pass into the blood stream.

A few attempts were made to sample venous blood from the postcava below the renal vein, but the low blood pressure and the tendency for this vessel to pass into spasm has introduced difficulties. These can be overcome but the postcaval wall is so thin that bubbles within can be readily seen with the naked eye. The postcava, in fact, is a natural pompholygometer for testing blood from the hind quarters of the body and has been used in our standard experimental procedure in studying bubble formation.

ANIMAL TECHNIQUE

The cat is anesthetized with nembutal and the abdomen opened with little loss of blood. The viscera are pushed aside and covered with moist cotton to prevent evaporation, thereby exposing a considerable

* The word altitude used in this sense throughout this paper refers to a simulated altitude in a low pressure chamber.

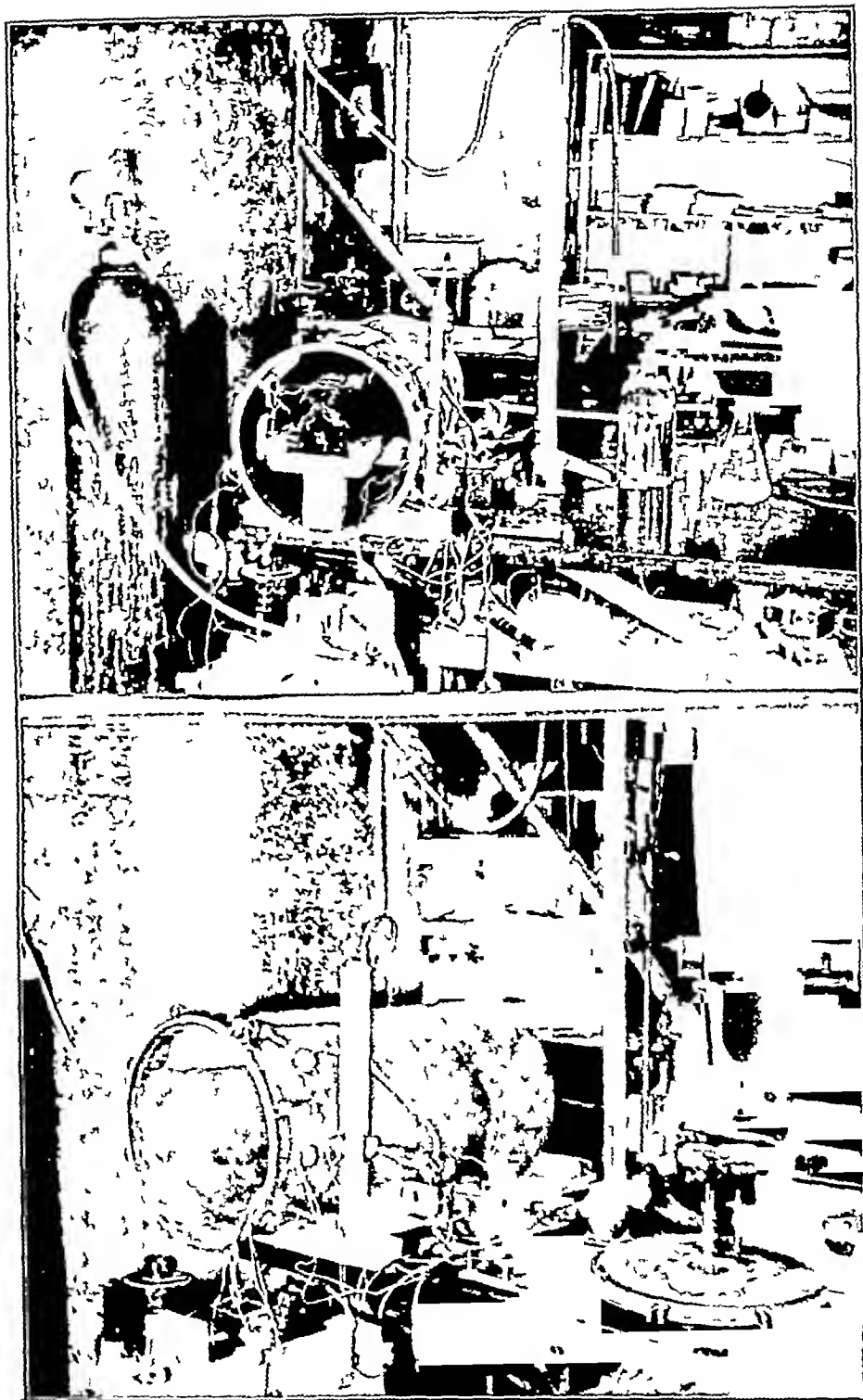


Fig 6 Above—View of high altitude chamber with cat in position, reservoir vacuum tank for rapid removal of air from altitude chamber, oxygen cylinder, mercury altitude gauge and accessory apparatus Below—Near view of same, showing mercury blood pressure manometer on outside of altitude chamber Equalization of pressure is effected by connecting open end with interior of chamber

length of the postcava together with its tributary branches. When the cat is placed in a horizontal position in the altitude chamber and well illuminated, observations can be readily made through the glass observation ports, and bubbles of 0.2 mm diameter can be seen within the veins. Only when bubbles are very large can they be detected in arteries.

The altitude chamber, shown in Figure 6, is an old autoclave, connected by a good-sized pipe and valve to a large reservoir chamber which can be evacuated with an air pump. The capacity is such that by opening the valve quickly or slowly the small chamber reaches the simulated altitude at any desired rate from explosive decompression to our usual average "rate of climb" of 5,000 feet per second.

The chamber is too small to admit a man and the altitudes are often so high that no man could exist for any length of time. Therefore, various devices have been developed for physiological manipulation from without the chamber. Some of these devices are shown in Figure 7. Blood pressure can be determined with a carotid cannula inside and a mercury manometer outside the chamber, provided care is taken to remove gas nuclei from connecting tubes. The open end of the manometer is reconnected to the altitude chamber for equalization of pressure as shown in the lower portion of Figure 6. Electromagnetic clamps for blood vessels or tracheae have been devised that will either open or close on making a contact, as well as automatic syringe for injecting solutions. Finally, an ingenious "mouse trap sectioner" for cutting the spinal cord with the cat in the chamber is activated by electromagnetic release of the spring of the trap to which a wire is attached that cuts through the cord.

Pure oxygen is administered by a glass tube fitting loosely over a tracheal cannula. The altitude has been mostly 45,000 feet (110 mm Hg), selected as a convenient high level at which cats would live for at least an hour with oxygen breathing despite considerable anoxemia. Under these conditions the rate and extent of bubble growth would be as great as possible.

RESTING ANIMALS AT ALTITUDE

If a series of resting nembutal anesthetized cats are prepared in this manner and observed for at least an hour at 45,000 feet, bubbles rarely appear in the postcava. Even at 50,000 feet where a percentage of the

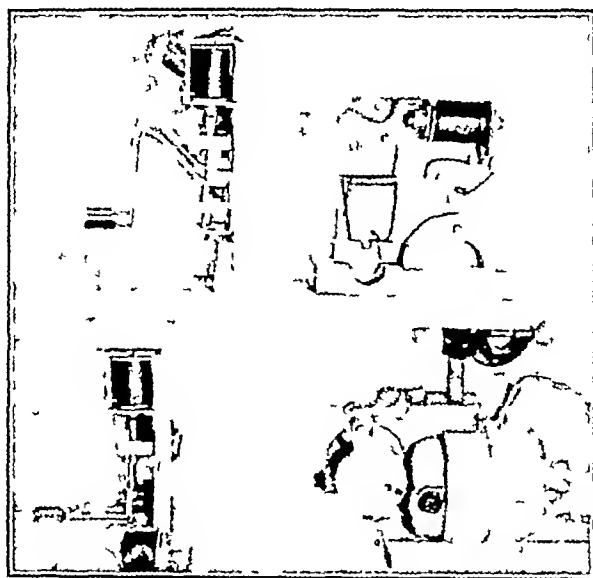


Fig 7 Various devices for manipulation in tank
Upper left—artery clamp closed by electromagnet
Lower left—artery clamp opened by electromagnet
Upper right—mouse trap spinal cord cutter Lower
right—motor and eccentric for passive movement of
leg

animals die, bubbles are not usually found during a 60-minute observation or during the life of the cat. Since dissolved gas in the animal is constantly and rapidly lost at this altitude by the efficient breathing and circulatory mechanisms, aided by further compensatory changes resulting from anoxemia, experiments were undertaken to retain the dissolved gas, expecting that bubbles might then appear. Both arteries (aorta and collateral arteries) and veins (postcava) were tied, or the leg was tourniquetted or the trachea clamped (when the heart continues to beat for 6-8 minutes), but even under these more favorable conditions, bubbles failed to appear.

ANIMALS STIMULATED AT ALTITUDE

However, if the hind legs of the cat were stimulated vigorously, bubbles from limb veins could be observed moving up the postcava, sometimes within 5 seconds of stimulation. By 16 minutes the great majority of the animals had formed bubbles although there was variation in time of appearance from cat to cat and an occasional animal was resistant to bubble formation and remained free of them despite this procedure. If only one leg was stimulated, the bubbles formed in

that leg and appeared in veins draining that leg only. This important discovery of the effect of muscle contraction on appearance of bubbles was first made by Whitaker, Blinks and collaborators,* using bullfrogs, and has its practical application in the well recognized fact that straining movements and exercise among aviators is the most important predisposing factor for the development of bends and chokes.

Another point of special interest is the variability in time of bubble formation in cats, which has its counterpart also in the varying resistance and susceptibility to decompression sickness observed in men. Part of this variability may be due to force and extent of muscle contraction on stimulation, part to differences in the circulation and part to the fat content of the animals, for it is well recognized that fat men are particularly susceptible to bends after diving and Boycott and Damant⁸ found a correlation between fat content and bends in goats after an exposure to compressed air. Since nitrogen is about five times more soluble in fat than in water, a large volume of gas is available for growth of bubbles in fatty regions.

To test the effect of fat content and bubble formation at altitude, the fat of the subcutaneous region below the diaphragm (including the inguinal fat pads and deposits below the skin of the legs as well as the popliteal space) was removed from more than 400 cats, weighed and then expressed as a percentage of the body weight. When time of bubble appearance was plotted vs. fat content, no correlation could be detected, a result we believe to be connected with the rather rapid appearance of bubbles after the muscles are stimulated. Only when the bubble formation is relatively slow, as on decompression from critical excess air pressures, have we observed a correlation between time of bubble production and fat. It is under these conditions that the slow seeping of additional nitrogen from fat deposits can make itself felt. Fat does not appear to be a primary cause of variability.

If stimulation of the hind legs is made at 35,000 feet (180 mm Hg) bubbles also appear but they are smaller and often hard to see. At lower altitudes we may expect to find minute bubbles of microscopic dimensions too small to do any harm.

ANIMALS STIMULATED BEFORE ASCENT

Evidently stimulation of the legs at altitude increases the ΔP above

* Private communication

that due to the altitude itself, so that bubbles appear in consequence. Such an increase in ΔP must enlarge gas nuclei even at ground level, and it is conceivable that the enlarged nuclei might persist for a sufficient time to give rise to bubbles if the animals were subsequently exposed to high altitude. We have a comparable experiment in a glass tube filled with water and free of any gas nuclei that can grow to visible bubble size at 45,000 feet (110 mm Hg). If the tube is hit a few blows at ground level, no bubbles may be visible but when immediately evacuated to 110 mm Hg, bubbles appear. If there is a delay before evacuation the gas nuclei disappear and bubbles will not form.

The analogous experiment succeeds in the animal. When the hind legs of cats were stimulated once a second for twenty seconds and the animals immediately taken to 45,000 feet, bubbles appeared in seven out of ten cats. However, if there was a wait of ten minutes before ascent to 45,000 feet, in only two of ten cats did bubbles appear. During this wait the enlarged gas nuclei in the animals had returned to their original condition. It is therefore apparent that vigorous muscle contraction and straining movements should not be carried out just before ascent, because, due to the excess ΔP , gas nuclei will be enlarged and may form bubbles at the altitude.

On the other hand, muscular exercise must have a beneficial effect in preventing bubble formation by virtue of the marked vasodilation and opening of closed capillaries in muscle tissue as well as the increased circulation and hyperventilation necessary rapidly to remove carbon dioxide from the blood. During exercise exactly those physiological mechanisms, naturally designed to remove a gas (carbon dioxide), are brought into play and they may be just as efficient in removing a gas such as nitrogen which is necessary for permanent bubble formation. The relative influence of these two opposing factors—the enlargement of gas nuclei by muscle contraction, and the increased gas elimination due to similar activity—will determine how much and how strenuous the exercise can be.

Actually, experience has shown that in man pre-exercise at ground level before ascent, even when combined with oxygen breathing, is not as beneficial as might be expected and little increase of protection is afforded over inhalation of pure oxygen at rest unless the exercise ceases some time before ascent. Moreover, the hyperventilation and additional oxygen required to make up the oxygen debt imposes an

excessive strain on the present oxygen mask and breathing equipment. In cats prestimulation with continued stimulation during ascent and at altitude does so increase the circulation and accelerate removal of nitrogen that visible bubbles are rarely observed in their blood.

In decompression after deep diving or other work under pressure, exercise has been advocated as a ready and efficient means of accelerating the removal of nitrogen. There are in fact reasons why this increase in ΔP from exercise is much less effective at ground level than at high altitude, reasons bound up with the mechanism of bubble formation during muscle contraction.

MECHANISM OF BUBBLE FORMATION AFTER MUSCLE CONTRACTION

It is obvious that an increase in ΔP , which we have defined as the gas tension, t , minus the hydrostatic pressure, P , may result either from an increased gas production or a decreased hydrostatic pressure, due to stretching of the liquid, i.e., to mechanical tension. Both factors are involved in muscle activity, the excess carbon dioxide and the mechanical tension of contraction. One of these factors, the decreased P , becomes particularly important at altitude because the animal is already near the vapor pressure of water (47 mm Hg) and the mechanical tension of muscle contraction may expand a gas nucleus to a large vapor cavity such as is shown in Figure 4. Dissolved gases would diffuse into this cavity at a rate depending on their relative concentrations and diffusion coefficients and the surface area of the cavity. The larger the vapor cavity, and the longer it persists before collapse, the larger will be the resultant bubbles. In previously air pressure treated cats at one atmosphere, with the same mechanical tension developed by muscle contraction, the decreased pressure may not reach the vapor pressure or may be only slightly below the vapor pressure so that a vapor cavity would be small and its persistence short. In this case the gas diffusing into the cavity would be far less, bubbles would be small and take more time to reach a visible size. In either pressure exposed animals or those at altitude, the high concentration of newly formed carbon dioxide from muscle contraction must greatly accelerate the early growth of bubbles.

Our conception of the mechanism of bubble formation during muscle contraction emphasizes both carbon dioxide concentration and mechanical tension, but, if the above reasoning is correct, the facts

point to mechanical tension as the more important of the two factors. Additional evidence in favor of mechanical tension comes from two types of experiment. In one, the legs of cats have been stretched without active muscle contraction and hence without carbon dioxide production, and in a second, lactic acid was injected so as to increase carbon dioxide without the mechanical tension. In a third type of experiment the muscles of the legs have been crushed and injured. The crushing must itself exert a mechanical tension on muscle fibers as well as mechanically stimulate them locally, with carbon dioxide production and acid of injury. Although its bearing on the theory of bubble formation during muscle contraction is not so clear cut, it has turned out to be a most effective method of inducing bubble formation. These three types of experiment may now be considered.

CRUSHED AND INJURED TISSUES

The first experiments on injured tissues were carried out by striking the thigh muscles of the anesthetized cat with a rubber hammer so as not to puncture the skin but to bruise and break small vessels, causing extravasation of blood in muscle tissue. The animals were then immediately taken to 45,000 feet altitude and in nine out of ten cats bubbles appeared in the postcava.

The blows might have resulted in bubble formation by setting up a series of pressure pulses as in the glass tube experiments previously described (p. 515). Therefore a crushing device was constructed for slowly squeezing the thigh muscles and actually tearing them, but without perforation of the skin, which might allow air to enter from outside. Again, when the cats so treated were taken to 45,000 feet, either immediately or after a wait of 10 minutes at ground level, the bubble formation was profuse. Bubbles could also be found locally in the injured region. These experiments indicate that bubbles might readily form and pass into the circulation of injured men at a high altitude.

The crushing procedure is such that very strong stretching forces are exerted on the muscle fibers, sufficient in some cases to actually break them transversely. This mechanical pull must play an important part in the bubble production, for it can be shown that injury to tissue containing no striated muscle is ineffective in forming bubbles, even when the volume of tissue injured is greater than in the muscle injury experiments. Thus, stripping the intestines, squeezing the kidney to a

pulp within its capsule, crushing the testes or bruising large areas of the skin have all failed to result in bubble formation when the cats were observed at 45,000 feet. Acid of injury and carbon dioxide must be formed in these tissues also (although possibly not in such high concentration as in muscle) so that the mechanical tension developed in crushing the muscle tissue would appear to be the important factor in formation of bubbles during muscle injury.

PASSIVE MOVEMENT AND STRETCHING

Passive movement of a leg can be attained by attaching the foot to an eccentric run by a motor, so that the leg is rapidly moved back and forth. Movement of this sort at an altitude of 45,000 feet does not give rise to bubbles. However, if a wire is attached to the ankle of a resting anesthetized cat, securely tied to its operating board, and the leg vigorously stretched at 45,000 feet, bubbles will appear, provided the blood supply to the leg is cut off by clamping arteries and veins. Without the vessel clamping, removal of gases by blood flow is sufficiently rapid to prevent bubble formation. Since the clamping of arteries and veins does not give rise to bubble formation without stretching, it appears probable that the mechanical tension is the cause of the bubbles.

LACTIC ACID INJECTION

Any local increase in lactic acid should liberate carbon dioxide from blood and imitate the excess carbon dioxide produced on muscle contraction. Therefore gas nucleus-free lactic acid was injected into the aorta, usually under conditions (clamping of proper vessels) that prevented its rapid removal by the circulation but insured its distribution to the hind quarters of the cat. These experiments have been carried out, both on cats previously exposed to air pressures of a critical value and duration (3.5 atmospheres for 2 hr.) such that bubbles ordinarily appear only a considerable time after decompression, and also in cats at an altitude of 45,000 feet.

In the cats exposed to compressed air collateral vessels were not clamped. The injection was made immediately after decompression and no bubbles were observed. In the "altitude" cats, injection was made just before a rapid ascent to 45,000 feet. In these animals bubbles appeared in nine out of twenty-one animals whereas in a control series injected with gas nucleus-free saline solution only one out of ten formed

bubbles. The difference is not significant when analyzed by the method of Chi square, but there is perhaps a trend, a tendency for lactic acid to favor bubbles, but not nearly as significant as the effect of muscle contraction itself. These experiments, combined with the leg stretching experiments, indicate that mechanical tension must be the predominant factor in the formation of bubbles.

COMPOSITION OF BUBBLES IN BLOOD

Analyses of gas bubbles in blood by the ordinary methods indicate a very high percentage of nitrogen. They have been considered nitrogen bubbles for all practical purposes. This is what might be expected from the tensions of gases at equilibrium in blood. However, when gas moves into a bubble rapidly, particularly into a rapidly forming vapor cavity, the composition of the gas left after collapse will depend mostly on the concentration of gas dissolved in the surrounding liquid, i.e., its solubility as at a given tension. Highly soluble carbon dioxide must be present in excess. If the bubbles could be obtained and analyzed while very small the carbon dioxide content would undoubtedly be high. This excess carbon dioxide must pass out of the bubble again and the final composition depends on gas tension rather than concentration. Therefore, in the early growth of a gas nucleus carbon dioxide may be very important, but for bubble persistence the nitrogen tension, represented by a partial gas pressure, is the determining factor.

When an animal breathes pure oxygen the nitrogen is flushed out of the body, but the carbon dioxide, which is a body product, remains at practically its original level. Carbon dioxide is also constant in an animal exposed to high air pressure, which dissolves an excess of nitrogen but the increased carbon dioxide pressure in the compressed air is small compared to the carbon dioxide produced by the body. Oxygen is always so rapidly used by the body that its tension is kept relatively low. Nitrogen becomes the important gas for permanent bubble formation and its removal essential.

THE EFFECT OF OXYGEN BREATHING

It is therefore not surprising to find that oxygen breathing for a sufficient time before ascent will completely prevent the formation of visible bubbles in the postcava of cats after vigorous stimulation of the hind legs. The actual time of oxygen breathing depends on the

strength of contraction With our standard 17-volt, 60-cycle, A C stimulus, one hour is sufficient to protect half the cats but one-half hour is not nearly enough If the stimulus is reduced to 6 volts, resulting in a less vigorous muscle contraction, the cats are fully protected after one-half hour of oxygen breathing

A weak stimulus will result in the development of a lower tension, both locally, due to fewer fibers pulling together at one spot, and generally, due to fewer muscles coming into play The end result is reduced hydrostatic pressure, which does not give a sufficient ΔP for bubble formation at the low nitrogen tension existing after one-half hour of breathing oxygen The greater number of muscle fibers contracting after strong stimulation will produce more carbon dioxide but because of the circulatory adjustments bound up with excess carbon dioxide production, the concentration of this gas will not rise proportionally The decreased hydrostatic pressure due to mechanical tension again appears to be more important than the carbon dioxide After one-half to one hour of oxygen breathing the nitrogen tension in the post-caval blood of cats is very low so that only gas in the most inaccessible and poorly vascularized places can be involved in bubble production

In man also, oxygen breathing before ascent will completely prevent the appearance of all symptoms of decompression sickness, and offers the most effective prophylactic treatment In man, the amount of oxygen breathing necessary has also been shown to depend on the extent of exercise at altitude The actual time of oxygen breathing to prevent bends in man and to prevent bubble formation in the blood of cats is about the same

Moreover, a comparison of nitrogen elimination curves from analysis of nitrogen tension in veins and arteries of man and cat show a surprising similarity in the actual time relations, despite the huge difference in volume of man and cat (30 l) In both animals also, the rate of nitrogen elimination during exercise is greatly increased The circulatory systems of man and cat appear to be so adapted that in man oxygen can be supplied and waste removed in approximately the same time as in the cat, despite the difference in volume of tissue to be serviced This adaptive relation is probably widespread among mammals of different mass and is no doubt connected with some basic property of cells, perhaps the time that certain cells can withstand lack of oxygen or the accumulation of injurious metabolites

THE EFFECT OF CIRCULATORY AND RESPIRATORY CHANGES

We have already seen that the circulatory and respiratory changes of exercise are perfectly adapted for rapid removal of gases but at the same time the muscle contraction of exercise, even at ground level, is an effective producer of bubbles. Some other method of increasing the circulation would be desirable to reduce the incidence of bends.

One, the use of drugs has not been thoroughly tested in the cat. Another, lack of oxygen, cannot be successfully applied to man but experimentally, in the cat, has turned out to be a fairly efficient method of reducing the bubble formation. When oxygen is withheld from the animals at 45,000 feet for some minutes before stimulation is begun, there is a significant difference in the number of cats in which bubbles appear, as compared with a control series receiving oxygen continuously. The hyperventilation of these anoxic animals is observed to be marked and we may presume that accompanying the hyperventilation there is the usual reflex vasodilation designed to supply muscle tissue with all the oxygen available. At the same time nitrogen is effectively removed.

THE SITE OF BUBBLE FORMATION

The wide variety of decompression sickness symptoms has led to the view that bubbles may form in almost any part of the body, and indeed, after an extreme compressed air treatment, bubbles are found in all regions of a cat, including arteries and veins, lymph vessels, eye humors and amniotic fluid, although not in the bladder urine. They are very abundant in fatty tissue and can be seen in veins draining fat deposits.

We have not determined whether these bubbles, which are abundant in the viscera, ever occur *within** the cells of the body but this is very unlikely. All attempts to detect bubble formation within single living uninjured cells (such as *Paramecia*, *Amoeba*, *Nitella*, sea urchin or starfish eggs) have failed. In some experiments the cells were saturated at a nitrogen pressure as high as 2,300 lb/in² and then decompressed. The outer surface of the cells was observed to act as a source of bubbles, but they never formed within, unless the cell was injured or dead. It is therefore doubtful that bubbles form within mammalian cells.

* Gerlach¹ has described bubbles within fat cells from guinea pigs (previously exposed to air pressure treatment) examined in sections prepared by the rapid freezing technique.

but they probably appear in intercellular spaces and would be most likely to form where one surface can be pulled away from another

In cats at an altitude of 45,000 feet, bubbles, after stimulation, are confined to the blood vessels and occasionally appear in lymph vessels. They are mostly found in veins, probably due to the lower blood pressure and greater gas tension (and hence lower ΔP) as well as direction of flow. Bubbles have never been observed in eye humors, urine or amniotic fluid, nor have they been observed around joints, although examination could not be made at altitude. At ground level this gas may have contracted to so small a volume as to escape detection.

In man numerous X-ray studies made in altitude chambers have disclosed the presence of air masses in joint cavities, in popliteal fat and in the fascia between muscles. All observers agree that air may be present in these regions without the pain of bends. It has also been observed that fluid can be injected into the bursa without giving rise to discomfort and gas in the bursa itself is not correlated with pain. Statistically, gas in popliteal fat and muscle fascia appears most likely to cause pain and we are led to the view that the undue expansion of gas in critical sensitive regions of connective tissue* stimulates sensory endings of pain nerves. Since localization of pain is not usually precise, it is frequently referred to the joint.

Another theory of bends pain refers it to the pain of muscle contraction in absence of oxygen, described by Sir Thomas Lewis²¹. Bubbles blocking the blood flow through muscle (true aeroembolism) would prevent access of oxygen and initiate conditions for the pain of anoxic contraction. However, the above mentioned X-ray photographs do not with certainty reveal bubbles caught in blood vessels. This fact, together with the observation that local pressure application or even a blocking of the blood flow by tourniquet above the painful region (which may also increase pressure by blocking venous return) will relieve bends, are both contrary to the intravascular embolism theory. They favor extravascular gas as the cause of bends pain.

Tension must be involved in gas formation in joints. Even at ground level some persons can develop gas in the shoulder joint by a proper rotary motion of the arm that puts strain on the shoulder. By a sudden pull on the fingers also, gas will appear in the finger joint as demon-

* Dr. A. C. Ivy informs me that he has a number of cases of bends where no gas could be detected in the roentgenograms.

strated by Nordheim.²² At high altitude the formation of gas under such conditions will be greatly facilitated.

It is impossible, from examination of the chest by roentgenogram, to distinguish excess gas in blood vessels from air in lung alveoli but several cases of chokes have shown an enlargement of the right heart which could be due to gas blocking the normal blood flow.* As shown by Van Allen, Hrdina and Clark,²³ and confirmed by our work on the cat, bubbles do not ordinarily pass the lung capillaries, due to the low pulmonary blood pressure, although they are able to pass systemic capillaries. We have frequently observed the heart of a cat to be distended with air from a rather copious bubble formation in veins when no bubbles could be found in arteries. It seems highly probable that air collecting in pulmonary capillaries could give rise to those sensations characteristic of the chokes.

Nervous symptoms are more difficult to analyze. They could be due to gas blocking capillaries of the central nervous system or to gas in nerve sheaths exerting pressure on nerve trunks. We do not know. Skin effects are also puzzling. Local bubbles in the skin have not been demonstrated. Frequently the skin rash will be distributed in a cutaneous area supplied by one sensory trunk, like the dermatome areas of herpes zoster. Possibly skin rashes, as well as the local anesthetics and hyperesthesias, are the result of nerve blockage, either central or peripheral. Some details remain to be filled in but on the whole the etiology of decompression sickness can best be expressed by one word—bubbles.

Private communication from Dr. Lax.

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THE THERAPY OF LIVER DISEASES*

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IF WE CONSIDER the many clinical syndromes which may be accompanied by various degrees of depression of hepatic function, it is apparent that the afflictions of the liver are almost as numerous and diverse as its multiple functions. In addition to a variety of diseases which affect primarily the hepatic parenchyma or associated biliary channels, there is a large group of metabolic, endocrine, and infectious diseases in which the major symptoms are referable to other organs, but which are often accompanied by marked alteration in hepatic function. Fortunately, the regenerative capacity of the liver is sufficiently great that few of the processes which produce alteration of hepatic function result in irreversible pathologic changes in the liver. A mere recitation and superficial description of the diseases which have been shown by clinical chemical methods to affect the liver adversely would require more time than has been made available for this presentation. The discussion will, therefore, be limited principally to a consideration of the most important organic non-surgical and non-malignant diseases of the liver, with particular attention given to current theories of basic therapy which may be employed in the treatment of these disorders. Some attention will be given at the same time to those aspects of the physiology and pathology of the liver which provide the rationale for current types of therapy. It should be emphasized at the outset, however, that in view of the extraordinary speed with which new information concerning the metabolic events occurring in the liver is being supplied from laboratories devoted to basic physiological research on this organ, any plan of therapy presented at this time must be modified and kept constantly in line with these advances.

A discussion of the problems posed by the therapy of non-obstructive, non-malignant diseases of the liver may be preceded by a statement concerning the general problems presented by those diseases which are

characterized pathologically by destruction of the hepatic parenchyma. Actually, until we are better informed concerning the nature of the various etiological factors at work in liver disease, we accomplish most in therapy by devoting our attention chiefly toward those measures which hasten repair of the damaged liver, regardless of the nature of the agent or process initiating the disorder. In obstructive lesions of the biliary channels or in affections of the gall bladder, attention is naturally focussed on the nature of the inciting agent, often with an eye towards its surgical removal. Here, too, owing to the fact that the parenchyma of the liver rarely escapes some degree of associated damage, the alert surgeon has come to pay increasing attention to the problem of hepatic reserve, and to those factors which accelerate regeneration of liver tissue.

The last decade has been particularly fruitful in providing information on the multiple factors which make for the maintenance of optimal liver function and on the agents which stimulate growth and repair of the liver parenchyma following experimental damage to the liver. A rational plan of therapy for the liver diseases will, therefore, fall short of the ideal in so far as it neglects to take into full account pertinent information in the fields of nutrition, physiology, and biochemistry, which has been made available within the last few years.

Since chronic liver diseases stem from preceding acute processes in the liver, it would seem wise to preface a discussion of the treatment of chronic liver disease by a brief account of the medical management of acute hepatitis. Strictly speaking, the term "hepatitis" is applicable to all syndromes which arise as a result of damage to the tissues of the liver, whether the provoking agent be chemical, physical, bacterial or viral in nature. According to some workers, the term hepatitis should also cover not only the degenerative changes which occur in the organ as a result of the action of these agents, but the reactive and reparative phenomena as well.¹ As subdivisions under this classification, one may place the various forms of hepatitis, such as acute, sub-acute, chronic and suppurative. A classification has been devised by Bloomfield² which depicts the various subdivisions in this scheme in a most graphic manner (see accompanying diagram). The classification proposed by Bloomfield is particularly useful in enabling the clinician to keep in mind the underlying sequence of phenomena in hepatitis, and to aid him in avoiding confusion from the older terminology. In Bloomfield's

scheme the variations which may occur in the course of hepatitis are represented by (1) Acute hepatitis progressing rapidly to death. In older terminology this would be referred to as acute yellow atrophy. (2) Acute hepatitis with apparent recovery, but with actual transition to a latent stage, with or without remissions. If clinical recovery does not follow, this may develop into a fibrotic stage, which is commonly referred to as cirrhosis. The third, and remaining group is composed of those cases in which hepatitis is latent from the start, and is masked clinically until incipient liver insufficiency supervenes. The analogy of this classification to that which has been devised for diseases of the kidney is immediately apparent. It may be recalled in this connection that until a coherent and simple classification had been devised for affections of the kidney, rational plans for the management of kidney disorders were largely defeated by a chaos of speculation regarding the nature and site of the pathological lesions. In the development of effective therapy for cardiac diseases, cardiologists have learned long ago to keep an attentive eye on the physiological status of the myocardium, and to disregard for the immediate purposes of treatment the primary etiologic factors in these diseases. The liver, like other glandular organs, has only a limited number of ways to respond to a large number of injurious agents and phenomena, and there is no valid reason to assume that the resulting pathology, except in a few reasonably clear-cut instances of liver disease, such as yellow fever, chronic passive congestion, etc., bears any distinctive etiologic label. There is even less evidence that the resulting type of metabolic disturbance bears any relation to the initial inciting process. Therapy, therefore, in non-surgical lesions of the liver should be concerned mainly with hepatitis, and the type of therapy dictated largely by a consideration of the *stage* of the hepatitis, i.e., whether it be acute, sub-acute, or chronic in its clinical manifestations.

The primary factors of importance in the therapy of hepatitis in its acute stages can perhaps best be illustrated by a consideration of the disease, infectious hepatitis. There have been few wars during the past century in which infectious hepatitis, or epidemic jaundice, as it is commonly called, has not been responsible for a significant portion of the total illness of troops not arising directly from injuries sustained as a consequence of participation in combat.^{3 4} During the present war, epidemic hepatitis has assumed even greater importance, and although the

exact number of cases among all the combatant forces of the world has not yet been revealed, there is sufficient evidence from published reports already available to lead us to believe that it is one of the more important non-combatant causes of morbidity among troops of all branches of the military service⁵

Epidemic jaundice, however, is by no means limited to members of the fighting forces. It has been a common disease in sporadic and endemic form among young adults in civilian communities for many decades. Boarding schools, educational institutions, orphanages, and other eleemosynary institutions, have been particularly favored as sites for outbreaks of infectious hepatitis, as numerous reports from this country and England testify^{6,7,8}. During the winter of 1921-22, the State of New York was visited over a very wide area by so-called infectious jaundice, with one report alone recording over 700 cases⁹.

The infective nature of epidemic jaundice has been clearly recognized for many years. Unquestionably the largest experiment of its kind attesting to the transmissible nature of infectious hepatitis grew quite accidentally out of an extensive program of immunization of members of the armed forces of the United States against yellow fever, with a vaccine made from chick embryo, to which a quantity of pooled human sera had been added¹⁰. Several recent communications deal with transmission of a disease indistinguishable clinically and pathologically from infectious hepatitis following transfusions of blood and plasma,¹¹ and following the use of human plasma in an epidemic of mumps¹².

The once familiar syndrome of "catarrhal jaundice" is now regarded as identical with acute infectious hepatitis. Much of the confusion regarding this disease entity grew out of an uncritical acceptance of the original concept of acute infectious jaundice advanced by Bamberger in 1855, and strongly championed by Virchow in the decade thereafter⁵. This theory held that the initial lesion in catarrhal jaundice was a duodenitis, in some instances characterized by a mucus plug at the ampulla of Vater, followed by a spread of "catarrh" to the bile ducts with the subsequent obstruction of the biliary radicles. That the disease is one involving chiefly the parenchyma of the liver there is no longer any doubt¹³. It would appear that failure on the part of older pathologists to find primary involvement of hepatic cells in this disease was due mainly to their having been denied an opportunity to examine the liver during the acute stages.

Qualitatively the clinical features of the average case of infectious hepatitis are remarkably constant. There are, however, marked differences in the degree of severity of symptoms, ranging all the way from slight indisposition and malaise in some patients to a state of marked prostration in the exceptional case, not unlike that seen in acute yellow atrophy. In the majority of cases, a prodromal period lasting from 1 to 9 days precedes the appearance of jaundice. Occasionally it is longer, and in rare cases the prodromal period may occupy a period of 20-25 days. About 10 per cent of cases give jaundice as the presenting symptom with no other preceding clinical signs. In most cases, however, there is a well-defined prodromal stage characterized by lassitude and fatigue, nausea and almost complete anorexia. Frequently there are complaints of epigastric pain, but only rarely of pain in the upper right quadrant. Liver enlargement is present at some stage of the disease in nearly all cases showing moderate to severe icterus. The appearance of bile in the urine is observed by the patient in nearly every instance within a period of one to three days before the appearance of jaundice in the sclerae. Less frequently the patient will also have noted light or clay-colored stools during this period. Frank recrudescence of the disease, a state recognized by deterioration of the patient's condition during recovery, and leading to a return of clinical symptoms, may occur in the exceptional case.

A study of the metabolism and liver function in infectious hepatitis reveals extraordinary aberrations in almost all biochemical and physiological systems for which there are adequate tests. Except in the infrequent case presenting signs of chronic liver disease, all abnormal values for the various constituents of the blood and urine in patients with infectious hepatitis return to a normal range within 30 to 40 days. Numerous tests, covering a wide and diverse range of liver functions, have been applied to a study of this disease by many investigators. A consideration of the results obtained by various workers reveals a surprising correlation in the degrees of alteration shown by the various tests at any time during the course of the disease in any given case. In a consideration of the average case, it is hard to escape the conviction that the principal damage to the liver consequent to this disease occurs early, and that during the major part of the patient's illness we are observing only a sequence of phenomena having to do with regeneration of the liver parenchyma.

THERAPY OF INFECTIOUS HEPATITIS

Except in the occasional case, when the disease becomes chronic, or in the rare case which terminates fatally, infectious hepatitis is a self-limited disease. Spontaneous recovery, in so far as it can be detected by clinical or laboratory means, occurs in the majority of cases within 30 to 40 days after the onset of initial symptoms. Until more specific information is at hand concerning the infectious nature of this disease, we are forced to limit our attempts at therapy to those measures which are believed to hasten repair of the damaged liver. Lack of specific information concerning a rational therapy for infectious hepatitis, however, has not prevented the development of very fixed notions regarding therapeutic regimes, and the literature, including textbooks devoted to treatment, abound with specific guides often diametrically opposed in substance and character for the management of the acutely damaged liver. According to some schools of thought, all forms of fat are to be avoided. At the same time, a diet high in protein is strongly recommended. The dietitian who is able to plan a diet high in biologically active protein without at the same time including a liberal quantity of fat deserves more commendation for her ingenuity than for her consideration of the patient's appetite. Until adequate experimental evidence can be adduced showing that diets which contain a moderate amount of fat are injurious to patients with acute non-obstructive disease of the liver, it seems unwise to prescribe diets which provide as little as 25 grams of fat daily. Anorexia is often a troublesome factor in the management of the patient in the acute stages of infectious hepatitis. Diets which are largely free of fat contribute further to the anorexia, since they are particularly unappetizing. They are also low in calories and in fat-soluble vitamins in relation to their bulk. The dictum against the inclusion of fats in the diets of patients with infectious jaundice doubtless arose from a mistaken concept of the pathology in this disease. While obstruction of the finer biliary radicles may occur, the disease is one which affects primarily the hepatic parenchyma and not the major bile passages, as claimed by Virchow. Evidence that a diet high in fat may not be desirable in the management of the damaged liver is based on results with experimental animals in which it is claimed that liver regeneration and survival of the animals is hindered by the inclusion of large quantities of fat in the diet.^{14 15} There is no good evidence, how-

ever, that inclusion of moderate amounts of fat is harmful if an adequate intake of protein and carbohydrate are provided at the same time

That a diet high in protein is optimum for hastening repair of the liver is not universally admitted. There are reports, notably those of Mann and collaborators¹⁶ in which it is claimed that in the dog, liver regeneration is delayed by the administration of a diet high in protein. Recent experiments of Whipple and collaborators,¹⁷ however, in experiments on the regeneration of the liver after damage from chloroform, appear to have laid the ghost of diets low in protein, in the treatment of liver disease. All workers seem to agree on the value of a diet high in carbohydrate. Not only are diets high in carbohydrate indicated on the basis of the protective value of such diets against liver intoxication, but on a physiological basis as well. Widespread damage to the parenchyma of the liver may be accompanied by hypoglycemia, owing to low glycogen reserve. In these cases a high intake in carbohydrate may be necessary in order to maintain an adequate level of circulating glucose.

Much has been written lately concerning the use of the sulfur amino acids, notably methionine, in the treatment of liver damage due to widely different causes. The mode of action of methionine, as well as of other sulfur containing amino acids in providing protection against damage of the liver is not clear, although various hypotheses have been offered. These hypotheses vary all the way from the idea that the amino acids provide a source of readily available sulfur for direct combination with the noxious agent, to an indirect effect achieved through the lipotropic activity of the amino acid. In one laboratory it has been claimed that the protective effect of a diet high in protein against damage to the liver by chloroform can be attributed largely, if not wholly, to the methionine contained in the protein making up the diet.¹⁸ Several reports on the use of methionine in the treatment of infectious hepatitis have recently appeared.^{19,20} The results of these experiments may be summarized by saying that in no instance were the results conclusive. A final statement on the worth of methionine in the treatment of acute hepatitis must wait, therefore, the appearance of further reports on the use of this type of therapy.

Patients presenting symptoms of severe infectious hepatitis may pose special problems with respect to the maintenance of nutrition. The patient may show a complete disinclination to eat for a period of several days. Anorexia, combined with an extraordinary tendency to lose weight

in the disease, may make the maintenance of a positive nitrogen balance difficult. Although the plasma protein concentration may show only slight alteration, there is good reason to assume that in the absence of an adequate protein intake a significant depletion in the stores of tissue protein may develop. In some cases a fall in serum albumin may be masked by an accompanying rise in serum globulin, so that the total serum protein concentration may appear unchanged. Moreover, a decrease in plasma protein is often accompanied by hemo-concentration, so that hypoproteinemia may not be perceptible unless determinations of the plasma volume are made at the same time. In order to provide adequate protein nutrition in the exceptional patient with infectious hepatitis who is unwilling to eat, the parenteral administration of a mixture of amino acids, such as that in a reinforced casein hydrolysate, may offer a practical solution to this difficulty. Several brands of casein hydrolysate are available at present for this purpose by means of which the entire protein requirement of a patient can be met for many days if the clinical state of the patient makes such parenteral administration imperative. Amino acid therapy to be of maximum effectiveness, must be supplemented with sufficient carbohydrate and fat to meet the caloric needs of the patient. Carbohydrate and amino acids may be given intravenously as a mixture. Unfortunately, the use of fat parenterally has not yet been achieved practically, so that only the oral route is available at present for its administration. Parenteral supplements of vitamins are available if desired. Except in the occasional case, however, when anorexia may provide a special need for vitamin supplements, a diet high in protein and carbohydrate with moderate fat meets readily the daily requirements of minerals and vitamins.

Bed rest, or at least limited activity, appears to be of paramount importance in the treatment of patients with infectious hepatitis. Retarded convalescence, or even recrudescence of the disease may occur following undue physical strain or exercise. Marked physical exertion, exposure to inclement weather, and convalescence from other diseases have long been associated with an increased susceptibility to infectious jaundice.²¹ In this connection it may be recalled that in experimental transmission of infectious hepatitis to volunteers by means of filtrates of plasma from patients with the disease, physical strain incident to marching and manoeuvring was required in some cases to precipitate an attack.

The per cent of patients with infectious hepatitis who may be expected to develop signs of chronic liver disease is not known with certainty at the present time. In most groups the reported incidence has been low. However, objective criteria for residual damage were not met in many cases, or patients followed for long enough periods of time to have warranted the judgment that they had fully recovered. Establishment of adequate criteria to answer the question of whether or not residual damage to the liver has occurred following an attack of infectious jaundice is one of the many important problems which will tax the ingenuity of the post-war worker in the field of liver disease. Certainly a small number of patients may be expected to develop signs of chronic liver disease following an unusually severe or prolonged attack of acute infectious hepatitis. The syndrome seen in these cases is one characterized by mild jaundice and fixation of various hepatic functions at aberrant levels. The patient may recover in time or the disease may progress slowly and insidiously into a syndrome not unlike that of hypertrophic biliary cirrhosis, with or without ascites. In the treatment of these exceptional cases, those measures which have been found useful in the management of cirrhosis of the liver should be instituted.

CHRONIC DISEASE OF THE LIVER

A syndrome consisting of a hard, stony liver with ascites, was known to Erasistratus, of Alexandria, nearly three hundred years before Christ. The disease was described later by Morgagni, Baillie and others in communications which have subsequently become *medical classics*. The term "cirrhosis" was applied to the syndrome by Laennec because the nodules projecting on the outer surface of the liver were "fawn or yellowish russet" in color. Many forms and varieties of cirrhosis have been described, but from the standpoint of supplying a basis for therapy there is little to be gained in a recital of the essential pathological characteristics of the lesions of cirrhosis. All forms, however, may be said to have in common three attributes, namely (1) proliferation of connective tissue, (2) degeneration and death of hepatic cells, and (3) areas of regeneration of hepatic parenchyma.²² There is eventually, in all long-standing affections, proliferation of connective tissue in the portal spaces with growth and extension of fibrous connective tissue into the whole hepatic lobule. The final stages of cirrhosis are accompanied by fusion of the peri-lobular connective tissue around the hepatic lobules with

subsequent deformation of the whole architectural pattern of the liver

The pathogenesis of classical cirrhosis is obscure, and must remain so until more information is at hand concerning the development of the disease in its early stages and, perhaps, until it is possible to produce in animals a disease that is indistinguishable clinically and pathologically from cirrhosis in human subjects. It is an over-simplification of the facts to suppose that this has been done, although recent attempts with experimental dietary deficiencies have yielded results that permit us to hope that it may eventually be accomplished. Most students of the pathogenesis of classical cirrhosis agree that it is essentially a chronic diffuse inflammatory process which is initiated by an obscure type of injury, followed by proliferation of connective tissue in and about former sites of degeneration and necrosis.

For many years it has been the custom to regard fatty cirrhosis as a form of Laennec's cirrhosis. Indeed, Connor²³ has expressed the opinion that Laennec's cirrhosis is the ultimate outcome of a process of fatty infiltration. He has, moreover, described the various stages in which the syndrome described by Laennec is reached as (1) an acute fatty liver, attributable to alcohol in the main, changing slowly to a stage (2) of early but definite fibrosis, and finally (3) progressing to a classic nodular cirrhosis with reduction in size of the organ.²⁴ Recent experimental observations concerning the production of fatty infiltration of the liver with diets deficient in methionine and choline, and with rapid amelioration of the condition when the deficient agent is again supplied, make it appear that certain types of fatty cirrhosis belong in a separate category.

THERAPY IN CIRRHOSIS OF THE LIVER

Chronic liver disease, with insufficiency, has posed and continues to present, one of the most complex problems of therapy which the physician encounters. Innumerable therapeutic measures have been devised within the past century in an attempt to cope with the problem of hepatic insufficiency, and with little success. Old remedies included potassium iodide, calomel, and a variety of saline purges such as vichy water and magnesium sulfate. Bile salts and other measures calculated to stimulate secretion of bile were employed with indifferent success. For a time it appeared that much might be accomplished through the use of diuretics such as acid forming salts and organic mercurials. Both

surgery and medicine provided new techniques for the treatment of cirrhosis. On the assumption that toxic agents were carried to the liver by the blood, various operations were devised by which attempts were made to shunt the blood carried by the portal vein into the general circulation. The operation of Talma, in which collateral circulation was achieved by suturing the peritoneal surface of the liver to the parietal peritoneum, had, and continues to have its advocates among members of the medical profession. Diverse as were these procedures, they had one thing in common, in that they were devised to relieve the chief complication of cirrhosis of the liver, ascites. The disease was regarded as fatal from the outset, and no hope was expressed that anything could be achieved other than securing greater comfort for the patient, and perhaps postponing exitus for a short time. From the time of the ancient physicians, medical writers have given cirrhosis of the liver a universally fatal prognosis, and nothing that has been achieved subsequently in the modern management of these patients has done much to alter this fatalistic concept.

Alcohol has always held a prominent place in the list of etiological factors proposed for cirrhosis of the liver, and as such has been particularly eschewed by the physician in planning a therapeutic regimen for his patients. The role of alcohol in the production of cirrhosis of the liver is still anything but clear. It would seem, however, that if alcohol is an important etiological factor in the production of the disease, that it is not due to its inherent toxicity for the liver, but rather to the factor of an associated disturbance in nutrition which is often an integral part of the syndrome of chronic alcoholism.

Attention was first directed to the role of faulty nutrition in the production of human cirrhosis of the liver by the studies of Rao, who in 1933 showed that a high incidence of this disease occurred among members of the population of Southern India, where alcoholism is all but unknown.^{25 26} In these areas nutritional deficiencies in protein, fat and vitamins, especially in vitamins A, C, and D, have occurred among members of the population for many years. In 1934, surveys made in Syria, where the incidence of cirrhosis is as high as it is in any part of the world, and where chronic alcoholism does not exist, showed that the diets of most members of the congested population were extremely low in protein. In Italy, in those regions where pellagra is endemic, the incidence of cirrhosis has always been high, as it has been in the southern

part of the United States, where pellagra has been a national problem since 1905. These facts, together with a growing awareness in this country of the relation between chronic alcoholism and vitamin deficiencies, have served to focus our attention on a possible nutritional basis for hepatic cirrhosis. This realization, together with a rapidly growing background in the production of experimental chronic liver disease in animals on diets low in protective substances has completely reoriented our therapeutic approach to the management of this distressing disease within the past several years.

Until the turn of the century, the diets prescribed by most physicians for patients with cirrhosis of the liver were generally low in all constituents. Carbohydrates were avoided because it was felt that excessive intestinal fermentation might arise, and prejudice the patient's clinical condition. Moreover, diets high in carbohydrate gave rise to diarrhea in many patients with chronic liver disease, thus providing another troublesome complication. Protein was avoided because it was believed that a damaged liver should not be further embarrassed by giving it protein to metabolize. Fat, too, was avoided on the basis that it would "stir up the bile" and add an additional load to the liver thereby. It is interesting in this connection to point out a rather glaring inconsistency, in that magnesium sulfate was prescribed at the same time in order to promote biliary secretion and drainage of the liver. Rationale for these various dietary restrictions were based on the knowledge of the central role of the liver in the breakdown of the constituents of food, and the belief that the liver should be "splinted" as it were, for the duration of the disease.

Around 1920 experiments were performed which showed that diets high in carbohydrate afforded a measurable degree of protection against intoxication with certain hepatotoxic agents, such as chloroform, phosphorus, etc.²⁷ These observations ushered in the first really important change in the treatment of chronic liver disease from that which had been in vogue for many decades. The results achieved by Mann, who claimed that liver regeneration was depressed in dogs by diets high in protein, appeared for a time to call for diets low in protein, but sufficient carbohydrate was permitted to provide for a normal or even high total caloric intake.

Rationale for the administration of diets high in protein has been supplied from several fields of investigation. The importance of protein

in protecting the liver from damage was shown by Goldschmidt and his co-workers²⁸ in 1939 as a result of their dietary studies on rats, when it was concluded that a diet high in protein given before the production of prolonged chloroform anesthesia, reduced the incidence of hepatic cellular necrosis. Whipple and his associates¹⁸ confirmed this work, and concluded, moreover, that the effects of a diet high in protein, in protecting the liver from chloroform damage, could be duplicated by the addition of methionine, and to a lesser extent of cystine, to a diet low in protein. Sebrell and associates²⁹ also demonstrated that in rats with cirrhosis of the liver produced by a diet low in choline and protein, improvement in the gross appearance of the liver, with hyperplastic regeneration of liver cells, occurred following treatment with choline and casein.

The rationale for a diet low in fat in the treatment of chronic liver disease stems from many sources, some valid, and some highly questionable. Obviously in the presence of obstructive lesions of the liver, the inclusion of a diet high in fat would be unwise, since under these conditions fats are not effectively digested. Also, it is known that certain lipotropic agents, such as choline and methionine, are effective in affording protection against certain types of experimental damage to the liver only if the diet is reasonably low in fat. There is some doubt, however, that the rational treatment of chronic diseases of the liver necessarily calls for a diet which is extremely low in fat. In the first place, it is impracticable to give a diet high in protein which at the same time contains little fat. Moreover, fats are rich sources of vitamins A, D, and E, and certain essential unsaturated fatty acids. Again, while it is stated that diets high in fat are displeasing to the average patient with liver disease, diets which are extremely low in fat are equally unpalatable and unappetizing. Finally, there is little evidence that diets with a moderate content of fat are prejudicial to patients with chronic liver disease.

Patek and his co-workers³⁰ were among the first to conclude that patients with alcoholic cirrhosis are benefited by supplements of the vitamins. It may be questioned, however, whether we should fasten the label of deficiency disease on the syndrome of cirrhosis of the liver. Certainly it cannot be regarded as an example of the classic types of deficiency diseases, such as beri-beri, scurvy, or pellagra. There is some reason, however, to regard cirrhosis of the liver as an *intrinsic* deficiency disease, in which faulty metabolism of certain essential components of

the diet may give rise to a syndrome which resembles deficiency diseases in some of its outward aspects, but which unlike the ordinary deficiency diseases does not respond in any striking or specific manner to one or a combination of vitamins

The assumption that faulty metabolism of vitamins of the B-complex occurs in severe hepatic insufficiency is based thus far largely on speculation and analogy, since no convincing laboratory demonstration of this phenomenon has yet been made. Evidence that faulty metabolism of vitamin A occurs in patients with chronic disease of the liver is more convincing. Ninety-five per cent of the stores of vitamin A are in the liver, and analyses on cirrhotic livers for vitamin A levels reveal in many instances a concentration of less than 10 per cent of the normal amount. Patek and others³¹ have shown that defects in dark adaptation may occur in patients with chronic liver disease of long standing. Night blindness and disturbances in dark adaptation in patients with hepatic insufficiency, however, are not greatly improved by the administration of vitamin A alone. Doses of vitamin A which are completely effective in the treatment of nyctalopia in patients with normal liver function are almost completely ineffective in relieving night blindness of patients with cirrhosis of the liver.³² Beta-carotene, which is effective in uncomplicated nyctalopia, is also ineffective in the treatment of night blindness in patients with chronic disease of the liver. Since the liver is regarded as the only important site for the conversion of carotene to vitamin A, a part of the deficiency may arise as a result of the failure of the diseased liver to effect this conversion. Evidence of vitamin K deficiency in chronic liver disease is also excellent. This deficiency arises perhaps in part as a result of lowered absorption of vitamin K due to altered metabolism of the bile pigments, but chiefly it would seem, because of the faulty utilization of the vitamin by the liver. Only when considerable liver function remains in chronic disease of the liver is vitamin K effective in enhancing the prothrombin value. Patients with long-standing cirrhosis of the liver may develop a syndrome characterized by osteoporosis and osteomalacia. Here, too, although the clinical symptomatology is strongly reminiscent of chronic vitamin D deficiency, the syndrome is neither prevented nor cured by the administration of vitamin D.³²

Evidence, therefore, is good that faulty metabolism of the fat soluble vitamins may occur as a result of chronic damage to the liver. One is

tempted to speculate on the possibility that interference with the metabolism of the water-soluble group of vitamins also occurs in severe hepatic insufficiency, although more evidence is needed to provide proof that this phenomenon occurs. Although the assumption continues to be made on clinical grounds, no evidence as clear cut as that for the aberrant metabolism of the fat soluble vitamins exists for faulty metabolism of the vitamins of the B group in cirrhosis of the liver. That deficiency in the case of vitamins A, D and K is essentially intrinsic, in contradistinction to the classical type of deficiency arising from lowered intake of these substances, is revealed in the failure to achieve satisfactory reversal of the syndrome by providing an ample supply of vitamins A, D or K, either by oral or parenteral route.

In connection with the idea that in chronic liver disease there is faulty metabolism or activation of the vitamins, it is tempting to regard other metabolic aberrations in chronic liver disease as being due to the failure of the liver to achieve synthesis of specific catalytic proteins, such as the enzymes, in sufficient quantities to meet the demands of normal metabolism. Fibrinogen, prothrombin and albumin are examples of three proteins which have their site of synthesis in the liver, and the synthesis of which is materially depressed in chronic hepatic insufficiency. There are probably many more examples of essential proteins of which the rate of synthesis is lowered in chronic liver disease, but we lack adequate techniques for their demonstration.

Most specific catalytic substances, organic as well as mineral, appear to require special protein vehicles for proper intermediation of their functions. It is possible, therefore, that the type of deficiency which we have labelled intrinsic, for want of a better term, may arise not as a result of lowered intake of the prosthetic catalyst, but through a depression in the rate of synthesis of the specific protein carrier needed to render the catalyst effective metabolically. The thiamino-proteins, and the proteins required as vehicles for the flavin and pyridine compounds might serve as examples, a deficiency in the synthesis of which would result conceivably in the production of symptoms not unlike those observed in thiamin, riboflavin and nicotinic acid deficiencies, respectively.

Optimism with respect to therapy of advanced cirrhosis of the liver is nearly always met with the statement that since much of the defect in cirrhosis appears to be a mechanical one brought about by fibrosis

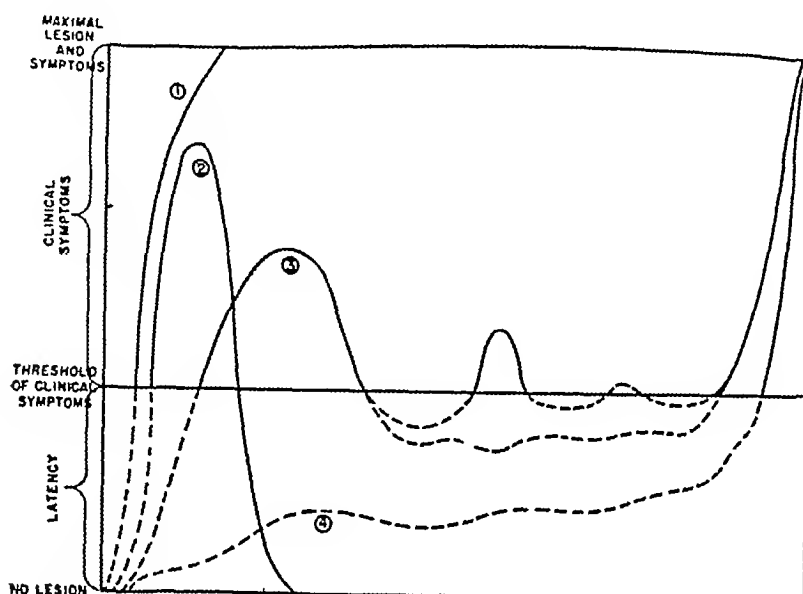
and atrophy of the liver, attempts to reverse the pathologic process are hopeless from the outset. Various explanations have been offered, for example, for the ascites which occurs in the chronic stages of disease of the liver, particularly of the Laennec type. The most common explanation for this phenomenon has been that of portal hypertension and consequent resistance to the flow of blood from the portal system through the liver. It is true that a portal hypertension may exist in many of these cases. It has been observed, however, that there are many instances when portal hypertension is marked in the absence of ascites. In other cases ascites has been recorded in the presence of a normal or only slightly elevated pressure in the portal system. Patek and Post³³ concluded that the ascites is related more directly to a deficit in plasma albumin, with consequent diminution in the colloid osmotic pressure of the blood. They have, moreover, concluded that when the concentration of albumin reaches 3.2 grams per 100 cc of plasma, ascites disappears rapidly, although no demonstrable change has occurred in the meantime in the portal pressure. Ralli, Hoagland and collaborators³⁴ have shown, however, that in cases which have been treated with a regimen of combined therapy, consisting of a diet high in protein and carbohydrate and the administration intravenously of large quantities of crude liver extract, ascites may disappear and the patient show marked clinical improvement for months before any demonstrable change has occurred in the level of plasma albumin. These observations suggest that the level of albumin in the plasma is not the sole determining factor in the production of ascites. In 1940 Robinson and Farr³⁵ reported the presence of an antidiuretic factor in the urine of patients with nephrosis and premenstrual edema. On the premise that a similar substance might be present in the urine of patients with cirrhosis and ascites, the antidiuretic effect of aliquots of dialyzed urine from the patients was studied by Ralli *et al*. Normal urine has only slight antidiuretic activity. The urine of patients with cirrhosis of the liver and ascites was found to possess a marked antidiuretic effect when injected into hydrated rats. However, there was little or no increase of antidiuretic substance over the normal in the urine of patients with cirrhosis without ascites. Moreover, the magnitude of the effect seemed to parallel the degree of ascites.

The antidiuretic substance excreted in the urine by patients with cirrhosis of the liver and ascites has its origin presumably from the posterior pituitary, although that this is actually the case cannot be

stated at this time That aberrant metabolism of other hormones may occur in cirrhosis of the liver is becoming increasingly certain It is also evident that aberrant metabolism of some hormones in chronic liver disease may arise through the inability of the diseased liver to accomplish their inactivation or alteration Certain changes associated with gynecomastia, and testicular atrophy in the male, in cirrhosis of the liver, are thought to arise as a result of the inability of the diseased liver to accomplish the inactivation of estrogen^{36 57} Free circulating estrogen is known to be high in cirrhosis, and it may well be that certain further changes having to do with aberrant water and electrolyte metabolism in patients with chronic disease of the liver may be attributed in part to a disturbed balance between the concentration of male and female hormones arising as a result of the inability of the liver to accomplish their proper metabolism

It would seem that many clinicians do not think that patients with active liver disease should necessarily be restricted in their physical activity Most physicians would not dream of permitting unrestricted activity in patients suffering from impaired function of a comparable degree in other organs, such as the lungs or heart Rest and freedom from undue physical activity is accepted as correct management in patients presenting signs of cardiac and renal insufficiency Yet many practitioners fail to treat acute or chronic hepatitis, in which extensive damage to the liver is evident, with equal consideration That rest or restriction of activity at once reduces the functional demands on the liver is evident from a consideration of elementary principles of physiology Moreover, it permits careful control of the diet and medication to a degree not possible in the ambulant patient

Aside from general measures directed toward relief of hypoproteinemia and anemia by transfusion of blood and plasma, certain specific measures directed toward relief of possible intrinsic deficiencies have been advocated from time to time For example, marked symptomatic improvement often occurs in patients with chronic liver disease when an unrefined, water soluble extract of liver is administered parenterally For some time we have been engaged cooperatively with Elaine P Ralli of the Third Medical Division, Bellevue Hospital, in trying to evaluate objectively the effect of liver extract, given intravenously, as a form of replacement therapy in hepatic insufficiency^{27 34} For this purpose a crude water soluble extract of Cohn's liver fraction G has been prepared



Variations in the course of hepatitis I, 1, Acute hepatitis progressing rapidly to death, 2, acute hepatitis with recovery, 3, acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis, 4, hepatitis latent from the start until advanced liver insufficiency supervenes (Bloomfield, courtesy of Am J Med Sci)

at the Rockefeller Hospital which can be given with comparative safety in large quantities by the intravenous route, provided careful tests for tolerance and sensitivity are carried out beforehand. By use of the intravenous route large amounts of liver extract can be given without the marked discomfort attendant on the continued use of potent crude extracts of liver designed for intramuscular use. While preliminary results have been encouraging, it is much too early to claim any extraordinary merit for this form of therapy. In any case, it can be used successfully only in conjunction with a full regimen of therapy which includes diet, rest, and numerous supportive measures indispensable to proper management of patients with chronic liver disease.

In the foregoing review, an effort has been made to show the influence which recent information in the field of metabolism and nutrition has had on the development of our present concept of rational treatment for hepatic insufficiency. Although we are yet far from the ultimate goal of satisfactory therapy for the hepatic diseases, some definite progress has been made, and the hope is very bright that as more

information is secured concerning the metabolic processes at work in the normal and diseased liver, increasing success in the therapy and management of these distressing disorders will be achieved

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BULLETIN OF
THE NEW YORK ACADEMY
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NOVEMBER 1945

THE MEDICAL AND PUBLIC HEALTH
IMPORTANCE OF THE INSECTICIDE DDT

*Hermann M. Biggs Memorial Lecture**

FRED C. BISHOPP, Ph.D.

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Agricultural Research Administration, U. S. Department of Agriculture

I FEEL it a distinct honor to be invited to appear before this distinguished group of the medical profession and on this lectureship established to revere an outstanding physician. This appearance is regarded, not as a personal recognition of any particular contribution of mine, but as an acknowledgment of the part that entomology and entomologists can play and are playing in the important and expanding field of preventive medicine.

Perhaps this occasion is another evidence of the feeling that in this day of specialization the workers in a number of related fields must join hands in a cooperative effort to elucidate many disease problems and to apply the results of such research for the welfare of humanity.

Insect-borne diseases back through the ages have been a dominant factor in determining the fate of armies and the outcome of wars. It is therefore not surprising that forward-looking medical men and engi-

* Given April 5, 1945 at The New York Academy of Medicine.

neers of the Army and Navy gave early consideration to ways of meeting the need for more effective and practical means of combating these diseases and their insect carriers. The great progress that has been made during the last few years has been interpreted by many as resulting directly from the war. There is doubt in my mind, however, whether research is more productive under the pressure of war demands than in peace. Many of the recent advances in combating insects are prewar discoveries, or are based on knowledge gathered during peacetime, as in the case of insecticidal aerosols developed by Bureau of Entomology and Plant Quarantine workers, Sullivan, Goodhue, and Fales,¹ in 1940, and methyl bromide, developed largely as an agricultural fumigant a few years prior to the war.² True, war makes funds available and gives special purpose to research, provides a proving ground for its findings, and accelerates the development and utilization of discoveries.

Another force that is especially operative during war is that of education. This force is probably as virile and far reaching in preventive medicine as in any other field. The incidence of insect-borne diseases, with the serious efforts put forth by military authorities to control or prevent these diseases, has been a powerful educational influence. It has brought forcefully to the attention of our millions in the armed forces and their families the importance of these diseases and the preventive measures used against them. This broad interest aroused in preventive medicine surely should not be neglected in our further efforts in health education. This enlightenment has by no means been confined to the rank and file of the armies and to the nonprofessional men of civil life. It is more or less evident at higher levels in every branch of the military service. Many medical men in uniform have, perhaps for the first time, become aware of the magnitude and importance of preventive medicine and especially of medical entomological problems. Many medical schools have modified their curricula to include medical parasitology and other subjects of vital importance in preventive medicine. Even though it will be regarded by some of you as presumptuous on the part of a layman, I venture the statement that I sincerely trust these changes will persist, and that our medical profession as a whole will give increasing attention to disease prevention rather than to thinking largely in terms of disease cure.

Of course, disease prevention is an extremely broad and intricate matter involving nutrition, housing, transportation, general economic

conditions, and many fixed customs and habits, none of which are strictly medical. Responsibility in the field rests not alone on the medical profession, but involves many special groups and, in fact, the people as a whole. It is right and proper, however, that the medical profession and those working directly in preventive medicine should take aggressive leadership in research, organization, legislation, and education looking toward more rapid and general advancement of this field so vital to the people of the entire world.

INSECTS IMPORTANT IN PREVENTIVE MEDICINE

Insects and related arthropods rank high in importance to the health and prosperity of nations in both peace and war. Some of the world's most dreaded diseases, such as plague, epidemic typhus, and African sleeping sickness, are exclusively insect-borne. Likewise the world's most debilitating malady, malaria, is chargeable to insects. Then there is Rocky Mountain spotted fever, endemic typhus, scrub typhus, encephalomyelitis, yellow fever, dengue, relapsing fever, filariasis, kala azar, verruga, pappataci fever—a formidable array, for which insects, mites, and ticks are wholly responsible. Nor should we overlook the part played by insects in the carriage of many other diseases, such as dysentery, typhoid, and tularemia, the parasitic worms, and the trouble induced by direct attack of insects on man where no disease organism is directly involved, as in various forms of myiasis, stinging and biting pests, and those that burrow into the skin. Often worrisome forms of life, such as swarms of biting midges, mosquitoes, and fleas, may assume considerable importance in impairing efficiency and even health. The bothersome bedbug, the cockroach, the elusive flea, and the persistent chigger and seed tick, each receives its complement of profane epithets and exacts its toll of sleepless nights.

We are not inclined to associate with public health insects that carry or produce plant diseases, those that destroy vegetables or fruits, cereals, or sugarcane, or those that damage livestock or food products in storage. Yet they often are a dominant factor in decreasing food supplies, so that low-income groups, or even entire populations, suffer from malnutrition, and many die of starvation. Other effects of insects on human welfare, if not on health, are evident in the devastation of forests and grasslands, which increases the cost of suitable shelters and induces destructive soil erosion, floods, and forest fires. Thus by no means com-

pletes the picture, for insects feed upon our flowers and shrubs, gnaw holes in our draperies, rugs, and clothing, undermine our homes, feed upon our axe handles, and even interrupt communications by cutting down telegraph poles or burrowing through lead cables

But insects are not all arch enemies of man. Of the some 620,000 species described, probably not more than 55,000 are recognized as being injurious. Thousands of species might be classed as neutral, and other thousands are beneficial. Some insects prey on our enemy species as parasites or predators, some contribute by destroying noxious weeds, some by breaking down dead plants and animals, so that they are returned to the soil to serve as plant food, some work over and aerate the soil, and others furnish dyes for the fine arts, fibers for clothing, or food for beneficial wildlife, our livestock and man.

In this last category the part that honeybees and other insects play in producing food often goes unrecognized. Thirty important food crops depend largely or solely upon insects to pollinate them. Without this assistance we would have to get along without such things as squash and other cucurbits, apples, sweet cherries, plums, and prunes. Furthermore, many of our crops so essential for livestock, soil improvement, and prevention of soil erosion would be barren or produce very little seed. This is true of alfalfa, the clovers, and others.

This theme is an extremely interesting and important one, and has a vital relationship to human welfare and therefore to any extensive efforts that man may put forth in combating disease-bearing and other insect enemies.

INSECTICIDES NOT THE ONLY WEAPONS AT HAND WITH WHICH TO FIGHT INSECTS

The urge that everyone has to kill dangerous insects quickly and certainly, together with the publicity given to the insect-killing potentialities of the insecticide DDT, has diverted attention from the many other sound methods of combating insects. The enemy is so numerous, its modes of attack so diverse, and the danger of depending only on insecticides for control so grave that we must use every weapon at hand.

Only a few examples of the many ways of combating insects of medical importance other than by the use of insecticides are cited here. For mosquito control, drainage and other steps to eliminate breeding places are familiar examples. As is well known, elimination of manure

piles and accumulations of fermenting vegetable matter is far more important in combating houseflies and stableflies than the use of any sort of insecticide. Certain kinds of ticks can be controlled, or even eradicated, by the destruction or manipulation of their animal hosts.

INSECTICIDES A DIRECT AND QUICK WEAPON

In combating insect pests the use of insecticides has a strong popular appeal. We are loath to take action till the enemy is upon us, and by that time something drastic must be done. It is therefore fortunate that we have a number of dependable insecticides that may be called into play on short notice.

Our insecticide arsenal was badly affected by the war. Possible war needs for arsenic and demands for lead threatened for a time one of our major groups of weapons, the arsenicals. Copper demands depleted our supply of paris green and copper fungicides, shipping interference and adverse weather reduced supplies of vital military and household insecticides made from Kenya-grown pyrethrum flowers, and the Japanese soon took over Malaya and other oriental areas from which had come our major supply of derris, one of the plants from which the highly effective rotenone is derived. The reduction in pyrethrum combined with increased military demands was particularly trying because farmers had come to depend on this insecticide for controlling many pests of vegetable crops on which arsenicals and other materials dangerous to man could not be used safely. Furthermore, it left our householders and food handlers without ammunition in the spray gun, a device now found on almost every kitchen and store shelf. The Bureau of Entomology and Plant Quarantine and many other official and private groups not only put forth efforts to increase the culture of pyrethrum and rotenone-bearing plants on this hemisphere, but instituted a search for suitable substitutes for critical or scarce insecticides. Hundreds of synthetic organic compounds were tested against a number of insects. Some showed promise, but most compounds of this class have been found to be rather highly specific. Investigations were also pressed forward on synergists, i.e., materials that would accelerate or intensify the insect killing properties of compounds having insecticidal value. These investigations too have yielded worthwhile results. None of the materials or combinations studied, however, appear to equal the organic chemical, DDT as an all-round insecticide.

DDT AN OUTSTANDING DISCOVERY

The common name DDT is based on the generic chemical name dichloro-diphenyl-trichloroethane, but more accurately designated by the long chemical name 1-trichloro-2, 2-bis (*p*-chlorophenyl) ethane (formerly called 2, 2-bis(*p*-chlorophenyl)-1, 1, 1-trichloroethane). This compound was first synthesized by a German student, Othmar Zeidler, in 1874³. Like thousands of other materials synthesized at universities, it remained on the shelves as just another compound until the Swiss firm of J. R. Geigy, A.-G., in its search for mothproofing agents tested many compounds and among them DDT, which displayed distinct insecticidal value. Wiesmann of the Swiss Agricultural Experiment Station, in cooperation with this firm showed it to have merit in combating certain agricultural pests⁴ and in killing houseflies⁵. Late in 1942 a sample of the insecticide prepared by the Geigy Company, and called Gesarol Spray Insecticide, was sent by the Swiss firm to its American branch, which in turn submitted it to the United States Department of Agriculture for evaluation. A group of entomologists at the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine, headed by E. F. Knippling, soon proved DDT to have a remarkable destructive effect on body lice. Research work conducted under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development was already well organized, and a colony of thousands of vigorous lice upon which to test various materials was already established, hence the development proceeded rapidly. In the meantime the Army had placed in the hands of men taking part in the North African campaign an effective louse-destroying agent known as MYL powder, which had been developed by the same scientists. DDT, where properly applied, was found to have remarkable persistence, and was not subject to deterioration, as is the case with MYL powder, the principal constituent of which is pyrethrum. Furthermore, the grave problem presented by the shortage of pyrethrum appeared to have been solved.

Initial tests with DDT were conducted with caution, since the material appeared to be a nerve poison and it was suspected that possibly Germany had permitted the material to be shipped out of Switzerland in the hope that it might be used extensively on our troops and thus in some way adversely affect them. Extensive toxicological tests carried

out by the Food and Drug Administration and the National Institute of Health, however, failed to demonstrate any toxic effects from the use of a powder containing 10 per cent of DDT in the neutral carrier pyrophyllite. Accordingly, after rather extensive field trials involving civilians, troops, and prisoners, DDT powder was accepted for general military use against lice.

It was found that DDT used as a powder on the skin and garments would give protection against louse infestations for three weeks or longer. This material in the form of an emulsion could also be incorporated in the garments and fixed so firmly that it would not lose its insecticidal effect for periods as long as eight weeks even though the garments were washed at weekly intervals.

Extensive field trials of DDT were carried out by medical and sanitary officers in cooperation with the United States Typhus Commission, the Rockefeller Foundation, and local civilian agencies in North Africa. The difficulty of requiring people with various prejudices and religious beliefs to remove their clothing for treatment was met by the development of a simple dusting apparatus by which the powder could be introduced beneath the clothing.⁶ The proof of the efficacy of DDT in controlling an epidemic of typhus was soon forthcoming. The stage was set in Naples for a devastating sweep of the disease through the civilian population, which would undoubtedly have involved our troops. The epic curbing of this outbreak has been recounted on previous occasions. The effective organization set-up and the availability of ample supplies of DDT, which was applied to more than a million and a quarter persons in a few months, can be credited with this amazing result.

Some indication of the wide interest in DDT is shown by the tremendous number of articles on the subject that have appeared in print in the last 2 or 3 years. A survey of the literature by R. C. Roark has shown that about 600 articles have been published.^{7,8}

CHEMISTRY AND MANUFACTURE OF DDT

The original method of manufacturing DDT has been set forth briefly in a British patent assigned to J. R. Geigy, A.-G.⁹

"225 parts of chlorobenzene are mixed with 147 parts of chloral or the corresponding amount of chloralhydrate and then 1000 parts of sulphuric acid monohydrate are added. Whilst stirring well the temperature rises to 60°C and then sinks slowly down to room temperature,

the mass then containing solid parts It is poured into a great deal of water, whereupon the product separates in solid form It is well washed and crystallized from ethyl alcohol forming fine white crystals, having a weak fruit-like odour "

Results of early tests in this country with DDT were so promising that the chemical industry was encouraged to go into production as rapidly as possible, and every effort was put forth to make adequate supplies available to the military The material was placed under allocation by the War Production Board on January 1, 1944 (Order No M-340) However, as production was increased, new and more extended uses were found which continued to keep military demands ahead of production At present about a dozen chemical firms are producing this insecticide and, with the exception of relatively small quantities that are devoted to research, the entire supply of approximately 2,000,000 pounds per month is going into military uses

Technical DDT consists largely of the para-para isomer of dichlorodiphenyltrichloroethane, which some of the ortho-para isomer and ten of twelve other compounds The para-para isomer is the most highly insecticidal and constitutes about 70 per cent of the technical material, the ortho-para isomer makes up about 25 per cent, and the other compounds the remaining 5 per cent The refined or recrystallized product consists almost wholly of the para-para isomer and is designed as pure DDT This pure compound melts at 108.5° to 109°C The technical product has a melting range of about 25° , therefore, specifications covering purchases for military uses designate a setting point rather than a melting point It is set at not less than 88°C A number of compounds containing DDT have been put out by commercial concerns under various trade names, such as Gesarol and Neocid

DDT is practically insoluble in water, but dissolves readily in a number of organic solvents such as xylene, acetone, and chloroform Petroleum oils also dissolve varying amounts of DDT, the less refined these oils are, the greater is their solvent power Ordinary kerosene will dissolve approximately 5 per cent of DDT at room temperatures

For general insecticidal uses there is no need to consider material of high purity and thus add to the cost of production For special purposes, such as for incorporation in aerosol bombs, the use of refined DDT may be justified in order to minimize corrosive action on the containers

The investigations in the Bureau of Entomology and Plant Quarantine of the chemical make-up of technical DDT have yielded important information ¹⁰ Research chemists in the Bureau¹¹ have also developed a colorimetric method by which minute quantities of DDT can be determined which permits a more accurate evaluation of the residue problems such as on food and forage plants and in water

FORMULATIONS OF DDT

To get the highest insecticidal efficiency from any material it must be properly formulated to fit into the many conditions encountered DDT has been prepared in various mixtures as dusts, sprays, and aerosols, but much remains to be done in this field As has been stated, the simple mixture of finely ground DDT in pyrophyllite was first used in the field of medical entomology Since that initial step, many formulations have been prepared for diverse uses against insects of medical, veterinary, and agricultural importance These formulations involve numerous solvents, wetting agents, emulsifiers, and stickers, and various combinations including mixtures with other insecticides Proper formulation of insecticides not only makes them more effective, but also ideally at least, more economical, more convenient to ship and store, more easily applied, and less likely to have an adverse effect on men, animals and plants

Fortunately, for two of the major uses DDT can be very cheaply and easily prepared I refer to the dust mixture already mentioned for louse control and to kerosene or fuel-oil solutions for use as a mosquito larvicide Some difficulty has been experienced, however, with the DDT crystallizing out in the oil drums when the material is stored at low temperatures Since these crystals are not easily redissolved, it is desirable to add an auxiliary solvent, such as xylene or a heavier petroleum fraction

When the carriers employed in the sprays evaporate, beautiful crystals of DDT are left on the surface of sprayed objects The type of these crystals varies much with the carrier used, as does also the rapidity with which they are formed There is evidence that the type of crystalline deposit affects its insecticidal potency

METHODS OF APPLICATION

Naturally, methods of applying insecticides must be governed by

the nature of the problem. The stability, solubility, residual effect, and other characteristics of DDT make possible the use of many different methods of application and have suggested almost innumerable types of apparatus for dispersing it. These range from the simple hand dusting, as in control of lice on man, to the application to jungle areas, by huge aircraft, of dusts, sprays, and aerosols for mosquito control. They also include impregnation of clothing and other fabrics in an emulsion or solution, the employment of explosives in various devices, of special generators to produce thermal aerosols, of manually-operated aerosol containers with liquefied gas as a propellant, of atomizers of diverse types and sizes (some little larger than a fountain pen), of various types of sprayers and dusters, and even the use of an oil can or a paint brush. Automatic drip cans or impregnated sawdust or other material have also been used for treating mosquito-breeding rice fields, streams, and ponds.

Most of these dispersal devices are in an experimental stage, and no doubt many new ones will be devised. It is a fertile field for those with inventive abilities. Through all the experimental and practical work the need has been apparent for special distributing equipment to meet the diverse conditions encountered in military operations and those more fully recognized here at home.

The development of methods for aerial application has been and still is of absorbing interest. Since 1922, when the Bureau of Entomology and Plant Quarantine first experimented with airplane dusting of calcium arsenate for control of the boll weevil on cotton, little attention has been devoted to spraying devices. The high toxicity of DDT to many insects gives us, for the first time, a liquid material that can be economically applied from the air. The Husman-Longcoy equipment for use on a Cub plane has proved useful and a basis for the development of other equipment, especially for employment on larger fast-flying craft. Tests have run the gamut from the Cub to large bombers and from tanks holding 35 gallons to those holding 500 or more. The helicopter, autogiro, and dirigible have not been forgotten. Prior to this work little information was available upon which to base even a guess on the effect of speed, type of plane, place and character of discharge, and other factors influencing the break-up of liquids. Droplet size is a highly important item in insecticidal efficiency which we must watch

TOXICOLOGY

One of the first points considered in connection with the development of a new insecticide is its toxicity to man and higher animals, as well as to various lower forms of life beneficial to man. Therefore, as soon as the marked insecticidal value of DDT was determined at the Orlando laboratory, steps were taken to have its toxicological effect investigated by Dr. Herbert O. Calvery and his associates in the Food and Drug Administration and Dr. Paul A. Neal, of the National Institute of Health. Later, Dr. Robert A. Kehoe, of the Kettering Institute of the University of Cincinnati, and Dr. M. I. Smith, of the National Institute of Health, undertook supplementary work.

Some of the results of this excellent research have been published,^{12, 16} and no attempt will be made here to review them in detail. There is complete agreement among these workers that DDT acts as a nerve poison when ingested or absorbed, that its toxicity to different warm-blooded animals varies widely, but that its acute toxicity orally is not of a high order. For instance, the oral LD₅₀ (median lethal dose) for white rats ranges from 200 to 300 mg. per kilogram of body weight, depending on size and age, for rabbits about 500, for dogs about 200, and for mice about 400. In preliminary experiments carried out by Orr and Mott,¹⁷ horses and sheep showed no clinical evidence of poisoning when given DDT by mouth in doses of 100 to 200 mg. per kilogram repeated for several days. Sheep were given $\frac{1}{2}$ to 2 grams per kilogram of body weight as a single dose. The largest dose caused tremors for one day and loss of appetite for two or three days. Some cows showed tremors after the first feeding of 100 mg. per kilogram but recovered even when the dose was increased after a week to 150 mg. and after another week to 200 mg. Some of these animals when posted showed hemorrhagic spots on the heart and other viscera. These spots apparently disappear after a few weeks. It is characteristic of DDT poisoning that animals may develop tremors from daily doses, but that these may entirely clear up while the administration is being continued at the same level.

It was determined early by Dr. Calvery that no toxicity or irritation results from 10 per cent of DDT in pyrophyllite applied as a dust to the skin. This has been amply demonstrated by the free use of the powder by hundreds of thousands of troops and civilians in louse con-

trol DDT in solution, however, can be absorbed through the skin. This is particularly true of oil solutions. There was some fear that DDT solutions might prove toxic when used as sprays, and especially as aerosols, but extensive tests by the National Institute of Health showed that animals exposed to very heavy doses in strengths adequate to kill insects produced no ill effects if the animals were not allowed to lick the insecticides from their bodies.

Preliminary experiments indicate that DDT is rather poisonous to poultry and birds. Investigations being conducted by the Fish and Wildlife Service indicate that birds are more tolerant of DDT than mammals and that wild duck are especially resistant, but that snakes, salamanders, toads, and frogs may be killed by dosages in the upper range of insecticidal efficiency. Unfortunately, fish are markedly susceptible. This appears to be especially true of trout, and it is possible that they may be injured by feeding on insects dropping into the water after being killed by DDT. Apparently DDT is most toxic to fish when applied in colloidal suspension in water, with emulsion next, and surface applications of dusts and oil solutions least poisonous to them.

The chronic toxicity of DDT in various forms has not been fully evaluated, although relatively large daily doses can be tolerated over long periods, there is evidence of some cumulative effect and of slight sensitization in animals but not in man.

It may be concluded from available facts that DDT is much less dangerous to man and higher animals from direct toxic action than are many other insecticides, but it should be handled with care, especially to avoid ingestion and prolonged contact of oil solutions with the skin.

Among the insects there is a wide range of susceptibility. DDT kills both by contact and as a stomach poison. Some insects, such as the Mexican bean beetle and boll weevil are little affected by it when applied in practical doses. On the other hand, extremely minute quantities picked up by flies crawling over a surface sprayed months before will effect a kill, and as little as 1 part of DDT to 100 million parts of water will destroy certain mosquito larvae in the laboratory. Recent work by the Bureau of Entomology and Plant Quarantine indicates that 1 gamma (one-millionth of a gram) will kill a housefly.

PART PLAYED BY DDT IN THE WAR

There have been in circulation so many statements about DDT

and its insect-killing powers that it is logical to ask—just what is DDT doing toward winning the war? It seems unnecessary to dwell on the importance of insects as annoyers and disease carriers in large-scale military operations. History is replete with evidence of this. Napoleon's operations in the West Indies were definitely stopped and the whole history of that area, and perhaps of the United States, was changed by the yellow-fever mosquito, which killed more than three-fourths of his army. Louse-borne typhus and malaria have determined the outcome of many campaigns, likewise, fly-carried dysentery and typhoid have seriously interfered with many military operations and caused much suffering, as happened in our Spanish-American War.

The world-wide struggle in which we are now engaged has given opportunity for every insect-transmitted malady to attack naturally non-immune groups of men. Furthermore, fast transport, especially by air, makes possible the movement in a few hours of infected personnel and infected insects from continent to continent and from hemisphere to hemisphere. To cope with this situation the best entomological and chemical knowledge, the soundest medical judgment, and the highest engineering skill are demanded. The promptness with which threatening outbreaks have been quelled and the present low incidence of these diseases among our vast armies speak for the effectiveness with which these forces have been brought to bear on disease problems.

The success of the campaign against the typhus outbreak in Naples during the winter of 1943-44 was due almost wholly to this new insecticide. It would not be fair, however, to ascribe to DDT more than its rightful share of the credit for these remarkable results. Recognition must be given also to the highly effective organization and vigorous and persistent efforts of the Typhus Commission, the Medical Corps of the Army, the Public Health Service, the Rockefeller Foundation, and other agencies concerned. Nor should we forget the quiet, indefatigable researchers of the Orlando laboratory of the Bureau of Entomology and Plant Quarantine, who made this effective weapon ready for just such an emergency. Obviously, without a sound organization, appropriate educational work, and full cooperation, including that of line officers and the entire military personnel, it would have been impossible to set up delousing stations, each capable of treating 5,000 persons a day, and to round up from their underground habitations and delouse the families of Italians. More than a million and a quarter persons were treated dur-

ing that winter, and owing to the louse powder, supplemented with methyl bromide fumigation, practically no cases of typhus have occurred among our forces. The introduction into this country of lice and louse-borne diseases with prisoners of war, refugees, and returning troops, has also been prevented. The armies of Great Britain are also making use of DDT against lice, both as a powder and as a clothing impregnant.

Mosquito control is a major factor in the prevention of malaria, dengue, filariasis, encephalitis, and yellow fever, and DDT is coming to play a major role in combating these diseases in our war operations. True, drugs are of recognized value in suppressing and treating malaria, but no drug has yet been found that is a true preventive or a dependable cure. For yellow fever we have a preventive vaccine that gives our troops protection, but there are multitudes of susceptible people, both in this country and in other parts of the world, who are not vaccinated and we must depend upon fighting mosquito carriers, especially on aircraft and around airports, if we are to hold this dread disease at its present insignificant level. As for the other diseases mentioned, there is no known method of prevention other than through mosquito control.

Thus far DDT has been employed in only a minor way in the anti-mosquito work of the military, and not at all by civilians. It is commencing to strengthen our aggressive war on mosquito breeding in training centers in this country and in camps in stabilized areas. Its greatest usefulness, however, is in ridding beachheads of infected mosquitoes—in fact, all mosquitoes—at the critical landing period when head and bed nets and other mechanical protection cannot be used and usual antilarval measures cannot be employed. It seems almost incredible that on D-day a few sweeps of a fleet of bombers with an almost invisible discharge of DDT in oil can destroy practically every mosquito in the area and permit our forces to concentrate on the Japs without danger of malaria or dengue infections for at least several days.

As little as 1/10 pound of DDT per acre has been shown by the entomologists at Orlando to kill all larvae of the common malaria mosquito, *Anopheles quadrimaculatus* Say, under favorable field conditions. An application of 1 quart of oil containing 5 per cent of DDT to the acre, under ordinary conditions of vegetation, will kill all larvae of this species. Even under jungle conditions 3 quarts of this solution per acre, if broken into fine spray particles 20 to 200 microns in diameter, will kill more than 95 per cent of all mosquitoes, both larvae and adults in

the area. Dusts containing 10 per cent of DDT used at the rate of 1 to 2 pounds per acre gave a complete kill and reduced breeding for one to two weeks in moderate vegetation and longer in heavy vegetation. Wind and wave action soon terminate the residual killing effect of both dusts and oil solutions. In xylene emulsions DDT can be prepared and shipped in concentrated form and diluted with water as used. Such emulsions were effective against *Anopheles* and several species of culicine larvae in dilutions as low as 1 part to 20 million. As little as 1 part per million had a lasting larvicidal effect in rain barrels.

As yet DDT has not been employed in insecticidal aerosols in field operations. However, experimental work carried out by the Bureau of Entomology and Plant Quarantine both at Orlando and at the Beltsville Research Center, has shown that the addition of 3 per cent of DDT materially increases the effectiveness of the pyrethrum aerosol at the strength now used against mosquitoes, and against flies its killing power is greatly enhanced.

One of the most remarkable qualities of DDT as an insecticide is its persistence or residual effect. This characteristic may be the one that will give us the whip hand in malaria control. When DDT in solution or emulsion is applied to wood or canvas as a medium fine spray at the rate of 200 mg per square foot of surface, mosquitoes resting on such surfaces are killed in a few hours. This killing effect persists for several months. Its persistence is even more striking in the case of flies. It is possible to spray fences, buildings, and even vegetation around fly breeding places, and expect the flies to be killed as they emerge from their puparia and crawl upon such objects. The insects are excited after they have rested on treated surfaces for a short time, but even though they may fly away most of them succumb. Most mosquitoes normally rest on nearby objects for at least a short time after becoming engorged with blood. Some fly about and alight several times while they are seeking a blood meal. In sprayed rooms or tents this would appear to insure contact of the insects with the DDT crystals and resultant death before the completion of development within their bodies and introduction into susceptible hosts of the organisms of malaria, yellow fever, dengue, or filariasis.

The fly problem has been acute in a number of the war theatres. This was particularly true in North Africa and on some of the islands of the central and southwest Pacific. In the African operations house-

flies were mainly involved. In the Pacific blowflies have been most troublesome. Unfortunately, DDT was not available during the North African campaign, but it is now meeting an urgent need in the Pacific theatre. DDT sprayed from the air has done much to remove the hazards of fly-borne dysentery and annoyance from flies during landing operations. Applications from the air, supplemented by the spraying of tents, buildings, latrines, and equipment, and by the usual sanitary and other fly-control procedures, hold the fly population to a minimum.

The residual effect of DDT is particularly useful in combating flies. This was first brought out by Wiesmann's work in Switzerland.⁵ Concurrent work by the Bureau of Entomology and Plant Quarantine in this country,^{18,19} showed that 5 per cent of DDT in kerosene applied to wood surfaces in buildings would remain highly toxic to houseflies for four to six months, and that aqueous emulsions were equally effective. The type of surface, the presence of oils or grease and dust in the air, and other factors influence the duration of effectiveness. Incorporation of DDT in paints and varnishes holds little promise, but the material retains considerable killing power when applied in cold-water paints.

The excreta of animals to which DDT has been fed kills flies crawling over it and prevents maggot growth. DDT has also shown some possibilities for treating manure to prevent fly breeding.

DDT is remarkably effective against fleas, either on animal hosts or on the soil or floors upon which they develop. This effectiveness has been shown for the common cat and dog fleas, the Indian rat flea, the sticktight flea, and others. Some preliminary tests indicate that fleas on rats can be destroyed by spraying or dusting the rat runs with DDT formulations.

Although bedbugs are of little importance in disease transmission, their indirect effect on human efficiency through annoyance and loss of sleep is recognized. The effectiveness of DDT against these disgusting pests is almost unbelievable. A 5 per cent solution of DDT in refined kerosene, applied as a spray to infested beds and mattresses, not only kills the bugs actually struck but also persists for six or eight months so that any bugs coming in contact with the sprayed surfaces are killed.²⁰

Another group of insects that play a small part in disease distribution are the cockroaches. The action of DDT against these pests is not so

spectacular, but it is distinctly toxic to them. Work thus far indicates, however, that the standard sodium fluoride treatment or pyrethrum as a contact spray is more effective.

Ticks, almost down to the last species, may be considered potential disease carriers. Several species are especially to be condemned, since they carry such deadly diseases as Rocky Mountain spotted fever, tularemia, and relapsing fever, produce paralytic conditions, and in many instances sorely annoy and cause secondary infection through their irritating bites. In experimental work carried out by Gouck and Smith²¹ 5 per cent of DDT in aqueous emulsions was effective against various stages of the brown dog tick and larvae of the lone star tick on dogs, and emulsions containing 0.5 per cent of DDT sprayed on infested roadside vegetation gave a high degree of control of adults of the black-legged tick for at least three weeks.

Preliminary experiments with DDT in kerosene or fuel oil applied as a spray to areas infested with the sand fly (*Culicoides*) and the black-fly appeared to eliminate the adults for at least a few days. Such solutions painted on window screens also prevented the sand flies from entering.

Chiggers and other mites claim our attention by their transmission of scrub typhus and by the extreme itching of their toxic bites. Numerous fever and other systemic reactions occur, and severe secondary infections are frequent. DDT promises to be valuable in combating these pests.

WHAT DOES THE FUTURE HOLD?

Peacetime developments have been adapted quickly to war needs, and we must be as alert in turning the implements of war to postwar problems. Fortunately, in the field of clinical medicine practically all the equipment, drugs, and surgical techniques that are emanating from the war effort can be applied at once in peace time. This is almost as true in preventive medicine, though the adaptation may come more slowly.

Since the interest of both physicians and laymen in preventive medicine is now far more general than before the war, can we not grasp this opportunity to extend research in the causation and prevention of disease and to further the application of acquired knowledge in this field?

Are we as physicians, sanitarians, engineers, entomologists, and economists to be content with the dynamite of plague hidden in our western yard, with the presence in our South of myriads of pestiferous yellow-fever mosquitoes ready to scatter the dread black vomit and the pain of breakbone fever over our land? Are we to continue to condone the presence of millions of rats in our cities and villages, and on our farms, permitting them to harvest the fruits of our labor and, with their associates the fleas and mites, to debilitate our people with endemic typhus? How long are we to harbor among the poor, and too often among the affluent as well, the disgusting louse? We know that these parasites have brought death to millions, that they attack man exclusively, and that they cannot survive without our blood and the warmth of our bodies. We now know also that a single treatment of every infested person with DDT would eliminate these lice from the earth. Should we be content to look on complaisantly while emaciated millions drag their malaria-shackled bodies from neglected fields to tottering huts? These problems are a challenge to the world that must be accepted. I do not mean to depreciate the excellent work that has been done, but the urge is on us and in the immediate postwar period it would seem both desirable and necessary to quicken our efforts.

After the fall of Germany and Japan we will still be confronted with armies of dangerous insect enemies which in the long run may cause more suffering and death and economic losses than our present human foes. In this war on the insects DDT will, I am confident, occupy a leading place in the arsenal we must keep ever ready to meet their varied forms and diverse methods of attack.

Modern transportation makes all countries of the world close neighbors. Therefore, one of our first and continuing problems is to prevent the spread of dangerous insects and the diseases they carry. In this field DDT and pyrethrum aerosols and sprays, if properly applied in aircraft, ships, and trains, will do much to minimize this hazard. The insect-control work around hospitals housing returned veterans, as well as educational work, should go far in preventing any serious outbreaks of insect-borne diseases. The extended antimalaria program proposed by the United States Public Health Service in cooperation with State health authorities should further aid in preventing the introduction and spread of mosquito-carried maladies. It would also be taking the first long step toward that ambitious program suggested by Dr. L. L. Wil-

liams, Jr of eradicating malaria from this country In this program DDT, especially in the form of a residual spray, will be a major weapon

It is difficult to foresee the precise place that DDT may assume in the future In addition to the fields of application briefly mentioned above, one can visualize farms with contented livestock and cleaner dairy products through the use of DDT against hornflies, stableflies, and houseflies, also outing areas with less annoyance from punkies or sand flies (*Culicoides*), blackflies, and mosquitoes Insect destroyers of crops may be held in stricter control, thus helping to assure ample and economic food production which in turn means better general health and happiness

DDT appears destined to assume an important role in controlling sand flies (*Phlebotomus*) and thus reducing the incidence of kala azar and sand fly fever Likewise, through its use against these insects, the dread disease verruga may be controlled in Peru and Colombia Tick control will probably be materially accelerated by the use of DDT, and this material will doubtless find an expanded field of usefulness in combating flies of all kinds The Chagas disease situation in the Americas may be materially helped by the availability of DDT in postwar days and its employment against the kissing bugs that transmit that malady The persistence of this insecticide on vegetation suggests the possibility of its successful use against the dread sleeping sickness of Africa, as well as the persistent and infection-carrying eye gnats in various parts of the world This would mean a great boon to the peoples in many lands where chronic conjunctivitis, trachoma, and resulting blindness are so prevalent

Due regard must be had for the detrimental effect of DDT on beneficial insects and other forms of life when its widespread application is contemplated We must learn more about the general field of usefulness of DDT as an insecticide, and especially about its limitations Much remains to be done in the perfecting of formulas for diverse uses and methods and equipment for application

General James S Simmons, of the Surgeon General's Office, United States Army, has summed up his views on DDT as follows "I feel quite sure that the knowledge gained of this amazing chemical, constitutes the most valuable single contribution of our wartime medical research to the future health and welfare, not only of this nation, but of the world"²² Magic insect killer though DDT is, it must be applied

by the right method, in the right form, and at the right time Many writers have claimed too much for DDT It is not a panacea for all insect ills, but it should hold an important place in the preventive medicine of the future

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CLINICAL OBSERVATIONS ON THE TREATMENT OF VARIOUS INFECTIONS WITH PENICILLIN*

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THE purpose of this paper is to review some of the significant changes that penicillin therapy has brought about in the prognosis, course, and management of certain infections. Of necessity the discussion of the various diseases that I shall consider will be incomplete since an entire article could well be devoted to any one of them. An attempt will, however, be made to illustrate the more important features of penicillin therapy in pneumococcic meningitis, acute and chronic osteomyelitis, and acute bacterial endocarditis.

The material presented herein is based on the observation of cases treated at the Evans Memorial Hospital during the last three years under the direction of Dr. Chester S. Keefer, and on a study of the case reports submitted by various investigators to Dr. Keefer in his capacity as chairman of the Committee on Chemotherapeutics and Other Agents of the National Research Council.

PNEUMOCOCCIC MENINGITIS

The seriousness of pneumococcic meningitis is well known, for prior to the introduction of the sulfonamides its mortality was almost 100 per cent. With sulfonamide therapy the reported mortality rates have varied for the most part between 60 and 80 per cent, although better results have occasionally been obtained in small, selected groups of patients. It is well known that several factors influence the prognosis in this disease. Thus, the mortality rate is highest in patients under two and over sixty years of age. It is also higher in those cases in which

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From the Evans Memorial Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.
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meningitis follows pneumonia than in those in which it follows infections of the middle ear or paranasal sinuses, or in which no primary focus can be demonstrated

The mortality rate in more than 400 cases treated with penicillin that have been reported to the Committee on Chemotherapeutics and Other Agents is approximately 50 per cent. No difference could be demonstrated in the gross mortality rates between the patients treated with penicillin alone and those treated with a combination of penicillin and a sulfonamide. Until these cases can be more completely analyzed, however, this finding should not be considered as conclusive, since the results in smaller series of cases reported by Waring and Smith,¹ by Sweet and his associates² and by Brigadier Cairns strongly suggest that combined therapy is much more effective than treatment with either agent alone.

In their response to treatment, the patients with pneumococcic meningitis fell into four main categories. In the first group were patients who had fulminating infections or were treated late in the course of the disease. They were usually in deep coma and were obviously moribund when treatment was started. Heroic measures were ineffective, and death occurred in forty-eight hours or less despite the use of large doses of penicillin, sulfonamides, and in several instances type-specific antiserum as well. An example of the failure of intensive therapy to alter the course of a fulminating infection, is illustrated by the first case.

Case 1 C F, a 59-year old man, was making a satisfactory recovery from an attack of lobar pneumonia when eighteen hours before entry he developed a severe headache and shortly thereafter became comatose. On admission to the hospital the blood culture contained 42,000 colonies of Type VIII pneumococcus per cubic centimeter, and a culture of the spinal fluid, which was grossly purulent, revealed 100,000,000 organisms per cubic centimeter. Therapy was instituted within less than 1 hour after the patient reached the hospital, 20,000 units of penicillin was injected intrathecally through the lumbar sac and the same amount was given intramuscularly every three hours. Two and five tenths grams of sodium sulfamerazine was injected intravenously shortly after penicillin therapy was started. Twelve hours later a second lumbar puncture was performed and another 20,000 units of penicillin was administered intrathecally. An hour later after appropriate tests had

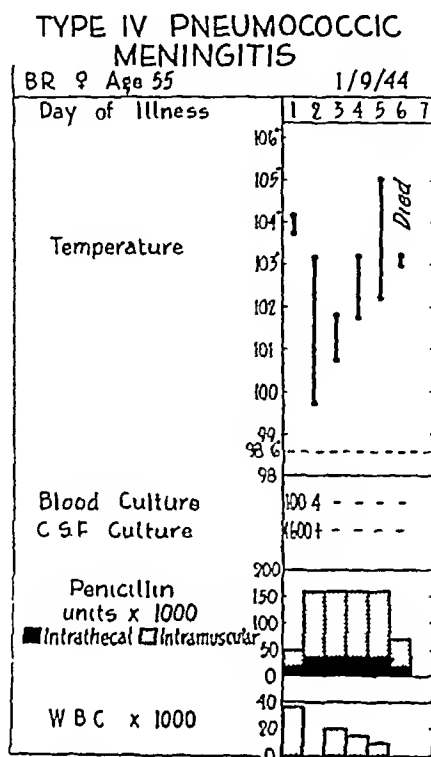


Fig 1 (Case 2) —Clinical course of a patient with pneumococcal meningitis who showed temporary improvement after the administration of penicillin. Cultures of the blood and spinal fluid became sterile but the patient died on the sixth day of the illness.

revealed no evidence of sensitivity the patient was given 100,000 units of Type VIII pneumococcus rabbit antiserum intravenously. None of these measures effected any improvement, and the patient died seventeen hours after treatment was started, thirty-six hours after the first appearance of the symptoms of meningitis.

The patients in the second group were also desperately sick and usually comatose, but during the first twenty-four to forty-eight hours of treatment some evidence of improvement could often be detected. Frequently the temperature became lower, and at the same time the organisms either disappeared from the blood and spinal fluid or were markedly reduced in number. After a brief period of apparent improvement, these patients rapidly deteriorated and died within sixty to one hundred and twenty hours after the beginning of treatment. At autopsy culture of the meningeal exudate was often sterile, and when positive cultures were obtained, the number of organisms found was usually insignificant. It has been believed that in these cases in which

the infection was obviously coming under control, death must be attributed to toxemia, or more specifically to damage inflicted on the central nervous system while the infection was still active. The second case is illustrative of this type of response.

Case 2 (Fig 1) B R, a 55-year-old woman, had had an acute otitis media and was admitted to the hospital five hours after she had developed a stiff neck. She was comatose at the time of admission, and treatment with penicillin was started within less than 1 hour. As indicated in the chart, the temperature fell and cultures of the blood and spinal fluid became negative twenty-four hours later. The patient remained comatose, however, and the temperature again rose. Consciousness was not regained, and 24 hours before death peripheral vascular collapse developed and persisted despite treatment with oxygen, plasma, and other resuscitative measures. Post mortem examination showed an abscess in the right parietal lobe and a layer of fibrinous exudate over the whole convexity of the brain. Cultures of the abscess, of the exudate, and of the ventricular fluid were sterile.

The third group of patients included those in whom continuing improvement could be demonstrated within a short time after the beginning of treatment and who progressed to an uncomplicated recovery. These patients were treated fairly early and were in much more favorable condition at the beginning of treatment than those in the first two groups. It was not unusual for the cultures of the blood and spinal fluid in such cases to become negative within twenty-four to forty-eight hours, and while further improvement was often slow, it was usually possible to predict at the end of four to six days that the patient would recover. The next case is that of a patient who made an uncomplicated recovery on combined penicillin and sulfamerazine therapy.

Case 3 (Fig 2) S B, a 37-year-old woman, was recovering from a mild upper-respiratory infection when twenty-two hours before admission she was awakened from a sound sleep with headache, nausea, and vomiting. Stiffness of the neck was first observed a few hours before entry.

On admission the patient was conscious but confused and restless. No source of the infection could be demonstrated. After eleven hours of treatment with sulfamerazine she became comatose, and therapy with penicillin was instituted as indicated in the chart. At this time

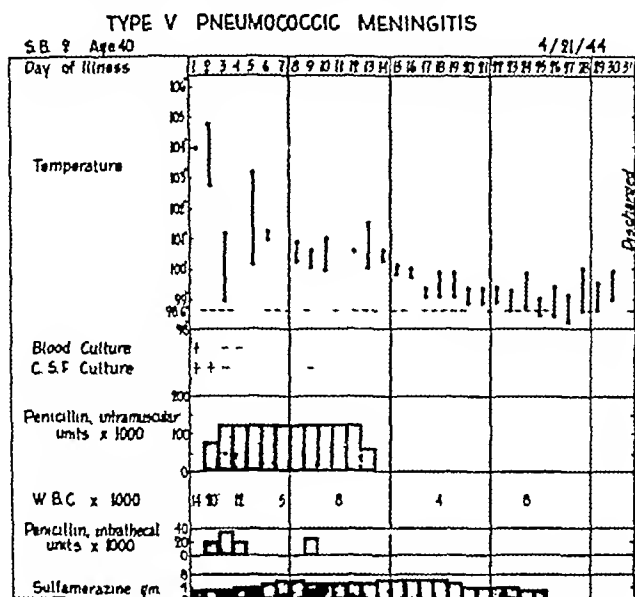


Fig 2 (Case 3)—Chart showing progressive improvement and ultimate recovery in a patient with pneumococcal meningitis who was treated with penicillin and sulfamerazine. The development of a complete spinal subarachnoid block on the fourth day of treatment was not accompanied by a relapse of the infection, presumably because of the effective antibacterial action of sulfamerazine.

culture of the cerebrospinal fluid showed two hundred and fifty organisms per cubic centimeter. Within 24 hours after penicillin was started the patient was conscious and rational, although her responses were slow. On the evening of the fourth day and for the next five days no fluid could be obtained by lumbar puncture. In view of the favorable course intrathecal therapy was discontinued. After thirteen days of treatment the patient was clinically well except for slight rigidity of the neck and the persistence of a low-grade fever. The penicillin was stopped but sulfamerazine was continued for another two weeks. The patient recovered without sequelae and has remained well.

The fourth group was comprised of patients who while apparently making satisfactory progress either relapsed or developed complications. Relapses occasionally occurred early, and were usually due to the development of a subarachnoid block that prevented the diffusion of penicillin throughout the subarachnoid space. This complication is illustrated by the next case.

Case 4 (Fig 3) H L, a 79-year-old man, developed a headache

MENINGITIS - PNEUMOCOCCUS TYPE XII

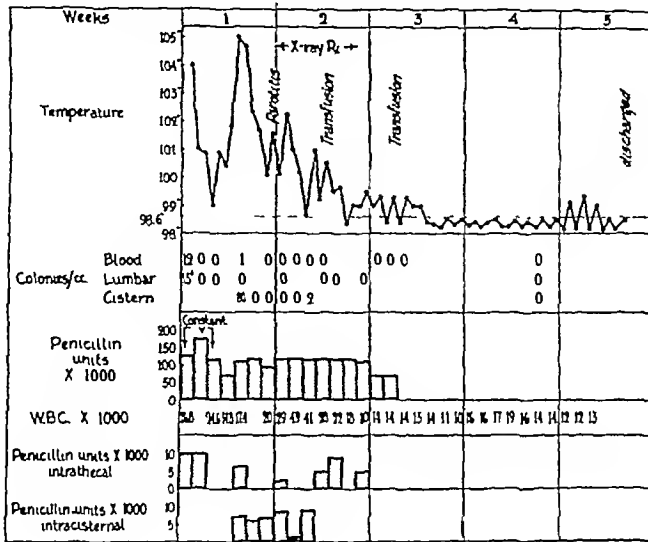


Fig 3 (Case 4) —Clinical course of a 79-year-old man with pneumococcal meningitis who was treated with penicillin alone. Relapse occurred on the fifth day of treatment following the development of a complete spinal subarachnoid block. The infection was again controlled when penicillin was injected into the cisterna magna and the patient progressed to a complete recovery.

and stiff neck, and treatment was started eighteen hours later. We were unable to discover the primary focus of the infection. On systemic and intrathecal penicillin the patient's progress was satisfactory until the third day, when the signs of a complete spinal subarachnoid block developed. Intrathecal penicillin was then discontinued until the fifth day, when a sharp rise in the temperature occurred and the patient became comatose. Penicillin was then introduced daily into the cisterna magna for a period of seven days, at the end of which time the block had disappeared and intrathecal administration by the lumbar route was resumed. The patient eventually made a complete recovery and has been well and working for two years.

As suggested by the experience with the previous case, the incidence of relapses resulting from the development of a spinal subarachnoid block may be decreased by administering one of the sulfonamides in addition to penicillin.

Relapses that occurred after treatment had either been discontinued or when the intensity of the treatment was being gradually relaxed were more frequent than those that appeared early in the

course of treatment The fact that pneumococcic meningitis is prone to relapse is well known, and many cases have been reported in which the patient suffered multiple relapses over the course of many weeks or months In patients who relapse, attempts to demonstrate an extrameningeal source of the reinfection are usually fruitless It is our belief that in such cases viable bacteria persist in the meninges, presumably in areas where plastic exudate is present We have arrived at the conclusion that, unless an extrameningeal focus can be clearly implicated, continued intensive treatment of the meningitis is a more rational course than a blind surgical attack on the mastoids or paranasal sinuses This view has also been expressed by Brigadier Cairns, who in a recent lecture on the treatment of pneumococcic meningitis with penicillin presented several excellent photographs of pathologic specimens demonstrating small foci of persisting intrameningeal infection that could well serve as the source for a reinvasion of the entire subarachnoid space

No data are available at present on which to base any estimate as to how many patients who recover from pneumococcic meningitis show residual damage to the central nervous system This sequela has been reported both in adults and in infants and children In the latter group the damage may not be apparent until sufficient time has elapsed to indicate that mental development is not progressing normally

The question as to what constitutes adequate penicillin therapy in pneumococcic meningitis needs further study Actually, each case presents individual problems, so that hard and fast rules cannot be laid down For most adults, the injection of 10,000 to 20,000 units intrathecally every twelve hours and the systemic administration of 100,000 to 200,000 units a day appear to be sufficient dosage to control the infection The concomitant administration of sulfadiazine or sulfamerazine in doses sufficient to maintain a blood level of free drug of 10 to 15 mg per 100 cubic centimeters also appears advisable

More difficult to decide is the problem of how long to continue treatment Both the clinical condition of the patient and the spinal-fluid findings may be misleading Relapses may occur after the temperature has remained normal for a week or more, after repeated sterile cultures of the spinal fluid have been obtained, after the spinal-fluid cell count has returned practically to normal, and after the spinal-fluid sugar has remained well within normal limits for several

days Because of the uncertainty as to when these patients are actually cured, we continue penicillin therapy for at least one week after apparent complete recovery and administer a sulfonamide for an additional two or more weeks

When the primary focus in pneumococcic meningitis is located in the middle ear or paranasal sinuses, the question of the surgical treatment of such a focus usually comes up for consideration The opinion most widely held at present is that the early surgical treatment of such foci has little effect on the course of the meningitis Energetic therapy of the meningeal infection in the majority of cases will also control the infection at the portal of entry In a few cases in which there is evidence of continuing infection at the primary site after the meningitis has been brought under control, surgical treatment of such areas can then be undertaken

ACUTE HEMATOGENOUS OSTEOMYELITIS

In acute hematogenous osteomyelitis the beneficial effects of penicillin on both the systemic infection and the local lesions of the bone and soft tissues has been repeatedly demonstrated Of the cases of acute hematogenous osteomyelitis treated with penicillin that have been reported to the Committee on Chemotherapeutics and Other Agents, recovery from the systemic illness has taken place in 95 per cent All these patients were seriously ill, almost half of them having staphylococcic bacteremia at the time treatment was begun It has been a common observation that in severe staphylococcic infections treated with penicillin toxicity frequently abates several days before the temperature returns to normal The usual course of events in acute osteomyelitis treated with penicillin has been for the patients to show marked improvement in their general condition, characterized by a return of appetite and a disappearance of lethargy and irritability within forty-eight to ninety-six hours The temperature may return to normal during this time, but more frequently it remains somewhat elevated for seven to ten days By the time it returns to normal, many patients appear to have recovered entirely from the systemic infection In a few cases with multiple metastatic foci, improvement has been slower and the patients have remained acutely ill for one to two weeks

With regard to the fate of the local lesion, information as to how many of these patients have recovered without the development of foci

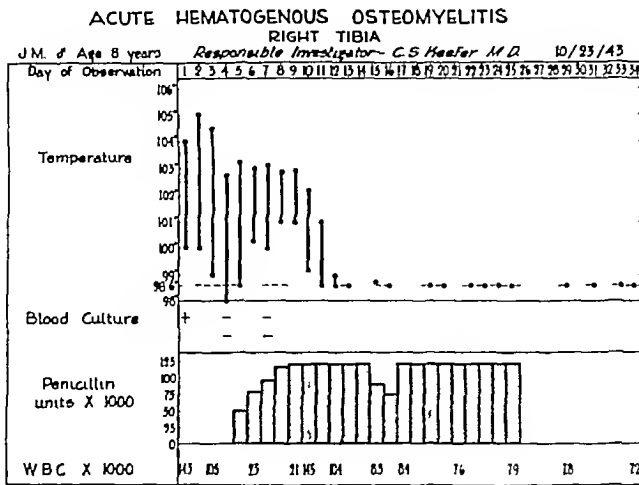


Fig 4 (Case 5)—Clinical course of an 8-year-old boy with acute hematogenous osteomyelitis of the tibia treated with penicillin alone without surgical intervention. The patient recovered completely and has remained well for 18 months without developing any signs of sequestration.

of chronic infection in the bone is not yet available. In the cases that we have observed the response of the local lesion has often been striking. In those that have been treated early, before a soft-tissue abscess has formed, the signs of acute inflammation have receded progressively, so that as a rule the affected part has appeared normal or nearly so after ten to twenty days of treatment. In the cases in which there has been progressive improvement, we have not believed that surgical intervention was necessary. On the contrary, we have been impressed with the fact that these patients recover more rapidly and more completely if surgery is withheld. Only rarely do they develop sequestra or draining sinuses that require later surgical treatment.

Case 5 (Fig 4) J.M., an 8-year-old boy, developed symptoms of acute osteomyelitis of the tibia three days before entry to the hospital. Four days of sulfathiazole therapy resulted in a clearing of bacteria from the blood stream, but the patient remained acutely ill and the local signs of inflammation were advancing. Although the temperature did not return to normal until eight days after the beginning of penicillin treatment, the patient's general condition was markedly improved within seventy-two hours, and during the same time there was distinct lessening of the local signs of acute inflammation. Pain and tenderness were almost entirely gone by the end of one week, although

some swelling of the leg persisted until two days before treatment was discontinued. The patient has been followed for 1½ years without developing any signs of sequestration or of a recurrence.

Even in patients who have been treated late—that is, after the infection has been present for a week or more—it has often been possible to obtain satisfactory resolution of the local process without resorting to surgery. In cases that have developed a definite abscess, if intensive penicillin therapy does not effect prompt improvement, it is desirable to evacuate the abscess and release pus from the intramedullary cavity through multiple drill holes. Recovery in these cases has been hastened by closing the incision by primary suture after placing one or more soft-rubber catheters in the wound for the local instillation of penicillin postoperatively. These catheters are clamped after penicillin is injected and do not act as drains.

In cases of acute osteomyelitis in which a suppurative arthritis exists, systemic treatment must be supported by intra-articular injections of penicillin if serious damage to the joint is to be prevented.

With regard to dosage, in acutely ill patients we now administer 25,000 units intramuscularly every two to three hours (200,000 to 300,000 a day) until the infection is well under control. After ten days to two weeks, if progress has been satisfactory, the three-hourly dose is reduced to 15,000 units. We believe that treatment should be continued for a week to ten days after the temperature has become normal and the signs of local inflammation have entirely subsided. This usually means a minimum of three weeks of treatment, in severe cases even more prolonged therapy may be necessary.

Judgment as to when to stop treatment must be made on purely clinical grounds, since the roentgenographic changes in the bone do not keep pace with the clinical course. Frequently destruction of bone appears to be greatest at a time when it is obvious clinically that the patient has recovered. This situation is illustrated in Fig 5, in which are shown three views of the femur in a child two years old. Treatment was begun about three days after the appearance of symptoms, and for the next twenty-four days the patient received 10,000 units of penicillin intramuscularly every three hours. The view on the left is that taken at the beginning of treatment, that in the center was taken just as treatment was being completed, and the one on the right was taken six weeks later.

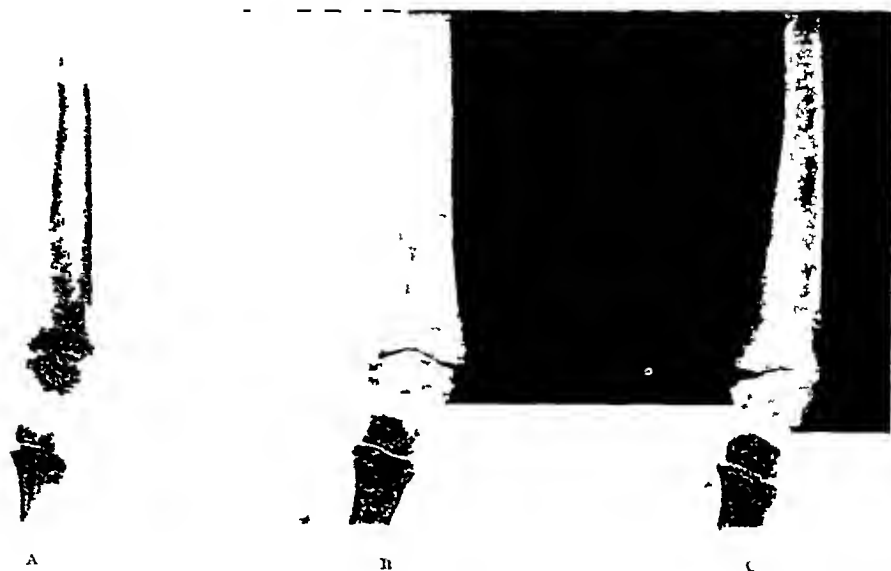


Fig 5—Roentgenograms of the right femur of a 2-year-old girl with acute osteomyelitis. The patient received penicillin for 24 days. No operation was performed. 5A—Roentgenogram taken at the beginning of treatment. 5B—Roentgenogram taken the day treatment was completed. Although roentgenographic evidence of bone damage was greatest at this time, clinically the patient had completely recovered from both the systemic and local infection. 5C—Roentgenogram taken 6 weeks after the completion of treatment illustrating the rapid repair of bone in the absence of further treatment after the infection had been controlled.

On the basis of the experience to date it seems safe to predict that with the use of penicillin acute hematogenous osteomyelitis will be regarded more and more as primarily a medical disease, although certain cases will still require careful surgical management of the local lesion.

CHRONIC OSTEOMYELITIS

Chronic osteomyelitis, on the other hand, must still be considered largely a surgical problem. In occasional patients the use of penicillin alone may result in a prolonged remission, but in the majority of cases experience has indicated that the combined use of penicillin and surgery is necessary to achieve the best results.³ The reasons for this are easily understood. Penicillin diffusing from the blood stream, or, after local application, from thick-walled sinus tracts frequently fails to reach bacteria that are present in scar tissue and sequestra, with the result either that healing does not take place or that if it does, viable

bacteria remain in the tissues and reactivate the infection within a short time

Without going into details, I should like to outline the program that we have now adopted for the treatment of chronic osteomyelitis. The development and execution of the surgical technique employed has been the work of Dr. Louis G. Howard, Chief of the Orthopedic Service of the Massachusetts Memorial Hospitals.

For four to seven days before operation, penicillin is administered intramuscularly, every three hours, in doses of 15,000 to 25,000 units. Prior to operation roentgenograms are taken after the instillation of lipiodol into the sinus tracts. Stereoscopic views of the injected tracts are particularly helpful in estimating the location and extent of the tracts and in demonstrating their relation to areas of active infection within the bone. At operation the sinus tracts are excised, osteomyelitic cavities are exposed, and the sequestra and granulation tissue contained therein are removed. At the completion of the operation one or more soft-rubber catheters are inserted in the wound, which is closed in anatomic layers without tension and without drainage. Postoperatively intramuscular penicillin is continued until the wound is completely epithelialized. Local instillations of penicillin are made through the catheters every twelve hours for seven to ten days, at the end of which time the catheters are removed. The sutures are removed at the same time, or more commonly a few days later.

We have now treated thirty-five patients with a combination of penicillin and surgery. The period of follow-up observation, varying from two months to two and one half years, is much too short to permit any conclusions regarding the final results, but the immediate ones have been quite satisfactory. In all thirty-five patients the local lesion healed, and in thirty-one it has remained healed. In several cases it was not possible to remove all sequestra, and the four relapses that occurred were not unexpected. Two of these patients are now well as the result of a second operation performed in conjunction with further penicillin treatment.

In chronic osteomyelitis, as in the acute form of the disease, the changes in the roentgenograms are of no immediate value in assessing the response to therapy. In adults, in whom the infection in the bone has been well localized for a period of years, little or no change may be seen in the roentgenograms even a year or more after treatment.

In children and adolescents, however, definite improvement is frequently seen in the appearance of the bone but not until several weeks or months after the completion of treatment

Even more significant than the response of the local lesion has been the effect of treatment on the patients' general condition. While some patients have shown little or no systemic reaction to their infection before treatment, many of them have presented the findings commonly encountered in a severe chronic infection, namely, poor nutrition, anemia, and weakness. Many of them have been unable to pursue useful activities because of their disease. Within the first month or two after treatment these patients have gained fifteen to twenty-five pounds in weight, their hemoglobin values and red-cell counts have returned to normal levels, and they have enjoyed a sense of well-being that they had not felt since the onset of their infection.

The most striking improvement that we have observed took place in one of the twenty patients treated with penicillin alone without surgery. This patient was a twenty-two-year-old man who had been ill for seven years with a chronic draining retroperitoneal abscess as well as a persistently active lesion in the femur. When he was first seen the liver and spleen were markedly enlarged and a Congo red test revealed 100 per cent retention of the dye in the tissues. Following two courses of penicillin separated by an interval of one year, the retroperitoneal sinus healed and drainage from the femur, which was not operated on, greatly decreased. At the completion of the last course of penicillin therapy, a Congo red test showed that only 57 per cent of the dye was retained in the tissues. In the next eight months the liver and spleen decreased in size so that they were no longer palpable. It is now a year and a half since his last treatment. The patient has gained seventy pounds and for the past year has been working full time without the loss of a day from work because of illness.

Before leaving the subject of chronic osteomyelitis, I should like to make it clear that we look on the patients in whom good immediate results have been obtained not as having the infection cured but as having it arrested. In most, if not all, cases viable bacteria are probably still present in the tissues, and given a suitable opportunity, the infection may well be reactivated. When relapses occur further treatment with penicillin and, if indicated, further surgical treatment should be carried out.

BACTERIAL ENDOCARDITIS

In discussing bacterial endocarditis, I shall confine myself primarily to a consideration of the acute form of the disease. The value of penicillin therapy in subacute bacterial endocarditis has been clearly demonstrated by the important contributions to this subject that have been made by several physicians in this city, notably the late Dr Dawson⁴ and Hunter,⁴ Loewe,⁵ McDermott,⁶ and MacNeal⁷ and their associates. The encouraging results that they have reported are familiar to all. Several problems remain to be solved, including those of the optimum dosage, the best methods of administration, and the value of adjuvant measures such as the use of anticoagulants, fever therapy, and the sulfonamides. One of the most interesting features of this disease is the absence of any clinical or laboratory criteria that will enable one to predict either before, during, or at the completion of treatment in which cases the disease will be permanently arrested by penicillin and in which it will be only temporarily suppressed. At the moment one can only follow the course of these patients. The finding of an organism that is susceptible to penicillin in a patient who is in good general condition does not necessarily ensure success, and the persistence of fever, embolic phenomena, splenomegaly, leukocytosis, and an elevated sedimentation for several weeks after the completion of therapy does not necessarily mean that treatment has failed. An extreme example of this statement is furnished by the following case.

Case 6 F M, a 29-year-old man, had had the symptoms of subacute bacterial endocarditis for fourteen weeks before admission to the hospital. He had lost 60 pounds and had become bedridden. The day before treatment was started he had a cerebral embolus, and as a result he remained stuporous and partially aphasic throughout the entire time that he received penicillin. At present he has no memory of ever having received the drug. Prior to treatment two blood cultures positive for *Streptococcus viridans* were obtained.

At the completion of treatment, except for the fact that the blood culture was negative, the patient had shown practically no improvement. Although the blood culture remained sterile, he continued to have fever until $7\frac{1}{2}$ weeks after treatment was completed. On the ninth day after stopping treatment, embolism of the right brachial artery occurred and new petechiae appeared almost daily for the next six weeks. Seventy-five days after treatment an enlarging pulsatile mass

over which a loud bruit could be heard, appeared in the right lower quadrant of the abdomen. It was thought to be a mycotic aneurysm of the right common iliac artery. It grew larger for ten days and then showed no further change in size.

It was not until six weeks after treatment was completed that we held any hope for this man's recovery. From that time on, however, his improvement was progressive. Six months after finishing treatment, he had regained his normal weight, there was no anemia, and the white-cell count and sedimentation rate were normal. For the last seven months he has been working full time as a draughtsman.

Acute bacterial endocarditis commonly involves previously undamaged valves and is usually caused by the ordinary pyogenic cocci, namely, the staphylococcus, the pneumococcus, and the hemolytic streptococcus, although cases due to other organisms are occasionally encountered.

It is well recognized that this disease manifests itself in two distinct forms—cases in which infection of the endocardium is primary and those in which it is secondary. In the primary form of the disease the patient presents the signs and symptoms of a constitutional infection without any evidence of localization. The blood culture is usually positive, but the diagnosis, particularly in the early stages of the disease, is difficult. Frequently it must be made by exclusion. The pathognomonic signs, such as the appearance of new or changing heart murmurs and the development of petechiae or other embolic phenomena, may be absent until late in the disease, and occasionally never develop. In such cases, the diagnosis may not be made during life, unless one is willing to conclude that the finding of one of the above organisms in the blood cultures over a period of several days in a patient who presents no signs of a localized infection is sufficient evidence for strongly suspecting the diagnosis.

Much more frequent is the secondary form of the disease, in which bacteria gain access to the blood stream from a frank focus of infection and only later become implanted on the endocardium. The diagnosis here may also be difficult, because again the pathognomonic signs are often absent and attention is usually fixed on the primary focus. It is not unusual in such cases for the diagnosis of bacterial endocarditis to be suspected only when progressive improvement in the primary lesion forces one to look elsewhere for the cause of the

patient's continuing symptoms and bacteremia

It is doubtful whether before the introduction of penicillin any patient with the unmistakable signs of acute bacterial endocarditis, other than a few patients with infections caused by the gonococcus, ever recovered. During the last two years several patients in whom there could be no doubt as to the diagnosis of acute bacterial endocarditis have recovered under treatment with penicillin. It is not unlikely that others in whom the disease has not been diagnosed have also recovered. The results reported to date indicate that the recovery rate from acute bacterial endocarditis is approximately 45 per cent in cases caused by the hemolytic streptococcus, 35 per cent in cases caused by the pneumococcus, and 25 per cent in those due to the staphylococcus.

Little is yet known as to what constitutes an optimum schedule of treatment in this disease. This derives partly from the fact that in contrast to subacute bacterial endocarditis, in acute bacterial endocarditis the issue is usually settled rather quickly. The patient either recovers or succumbs to his infection within a few days, and there is little opportunity to experiment with dosage. Likewise, the fact that in many cases the diagnosis has not been established until after the patient has died, or occasionally until after he has recovered, makes it even more difficult to investigate the value of various treatment schedules. The next case illustrates the fulminating course that many of these patients follow.

Case 7 M. R., a 45-year-old woman, had been sick for only four days prior to her entry to the hospital. The sole complaints were fever and headache. Physical examination showed numerous pustular petechiae, but no abnormal cardiac signs could be elicited. The blood culture showed 4,000 colonies of *Staphylococcus aureus* per cubic centimeter. Following the administration of 200,000 units of penicillin daily the blood cultures became sterile, but the patient grew steadily worse, developed anuria, and died in shock after five days of treatment.

Autopsy revealed the presence on the mitral valve of several fresh bacterial vegetations from which *Staphylococcus aureus* could be cultured. There was no evidence of pre-existing valvular disease.

It seems clear that in most cases prolonged and intensive treatment is advisable, but it is quite striking that an occasional patient has recovered after relatively brief courses of therapy.

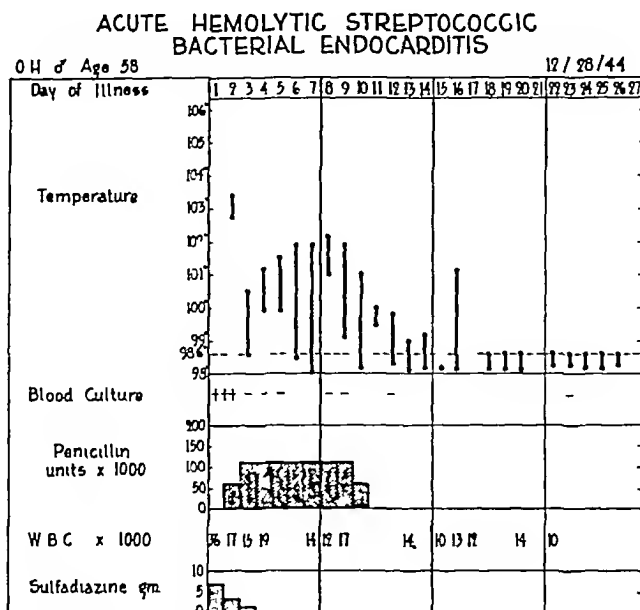


Fig 6 (Case 8)—Chart of a patient with acute bacterial endocarditis caused by a B hemolytic streptococcus. In this case an aortic diastolic murmur first appeared 22 days after the last positive blood was obtained and 13 days after treatment with penicillin was completed. This patient subsequently developed severe cardiac failure but no further signs of an active bacterial infection could be demonstrated.

In patients with acute bacterial endocarditis who have developed valvular defects, the appearance of severe cardiac failure after the infection has been controlled, has frequently constituted a serious obstacle to complete clinical recovery. Some of these patients have died within a few weeks or months from cardiac failure, others have remained seriously incapacitated.

One observation of considerable interest has been the fact that in several patients significant cardiac murmurs have not developed until one or more weeks after the infection has been eradicated and treatment has been completed.

Case 8 (Fig 6) O H, a 56-year-old man, developed an acute tonsillitis with high fever nine days before entry to the hospital. Sulfonamides were administered for five days, without improvement. On admission he was acutely ill. The only localizing signs of infection were a subsiding acute tonsillitis and minimal signs of bronchopneumonia in the left lower lobe. No cardiac abnormalities could be made out. Three blood cultures taken within the first twenty-four hours

were positive for beta hemolytic streptococci and intramuscular penicillin therapy at the rate of 15,000 units every 3 hours was begun and continued for eight days. At the end of this time the patient appeared to have recovered from his infection and the penicillin was discontinued. A low-grade fever persisted for a few more days and then disappeared.

The patient was allowed out of bed and was being prepared for discharge when on the twenty-third hospital day, thirteen days after the completion of treatment, a loud aortic diastolic murmur was heard for the first time. The patient left the hospital against advice three days later. Within three weeks he returned in severe cardiac failure, from which he was still incapacitated four months after the completion of treatment. Repeated blood cultures have been negative.

The appearance of aortic diastolic murmurs after the completion of treatment has been observed in other cases. Dr. Keefer has called attention to the fact that henceforth healed acute bacterial endocarditis, including both cases in which the disease has been recognized and those in which it has not been, will have to be considered as one of the causes of aortic regurgitation.

In conclusion, it can be said that the diseases discussed above are only selected examples of how the introduction of a new and potent chemotherapeutic agent may alter the course, prognosis, and management of disease. It is safe to predict that today we have only glimpsed the important changes that penicillin is going to effect in many of the common and uncommon infectious diseases encountered in medical practice.

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ON CERTAIN BIOLOGICAL FACTORS IN
HUMAN DISEASE *

GEORGE DRAPER

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As the vast discipline of medicine expands we can see ever more clearly how deep and complex are its bonds with the universe. For medicine deals with human disease and that in turn embraces man as well as his environment. The man is of special significance because he is the product of preceding eons during which, by slow and painful evolution, his fate has been determined. Those forebears who occupied lower branches on the tree of life struggled up from the ocean to gain a precarious hold upon the land. In the sea their bodily humors were at one with their environment, but as they came ashore protective mechanisms were devised to stabilize this inner medium which bathed their cells and to insulate them against an alien outer world. The adjustment to this change of atmosphere wrought hardships and provoked many varieties of biological design—some successful, others not. But one of life's main resources in its battle with a changing environment was its own infinite adaptability which has led to the complete individualization of each person. Through all these changes complexity mounted and after the establishment of an autonomic nervous and smooth muscle system which adequately mediated all the life-maintaining functions, the high if not always wise control by reason supervened.

In the past half century the transmission of all these accumulated characters has been shown to be effected by materials carried in the chromosomes of our germ cells. No man or woman can hope to escape the influences which flow from inherited chromosomal tissue, be they good or bad. Nor can the many protoplasmic products of these ever be expected to reach their appointed end unchanged. For the impressionable and reactive cell, within the limits of its nature, is inevitably altered to a greater or less degree by manifold forces from without. It

* Read December 12, 1944 before the joint meeting of the Sections of Medicine and Neurology and Psychiatry of The New York Academy of Medicine. From the College of Physicians and Surgeons and Presbyterian Hospital. Aided by a grant from the Rockefeller Foundation.

is because of the foregoing reasons that individuals differ in appearance and that each reacts in a different personal fashion to any stimulus. The effort to comprehend the mechanism of these variations and how or why they become part cause of human disease is a major challenge to medical biologists.

The three sick people who provide the text for this essay are stationed at different points along the arch which spans the whole range of clinical medicine. The first was a Greek cook who had never known a sick day in the forty years of his life. For three months before his illness his business had been going badly, but he had not informed his wife of this fact because he did not want to alarm her. He admitted, however, that he was greatly troubled and said, "When you figure you can't make ends meet, that's sufficient." At the start of his illness he developed ten boils on his left thigh but sulfathiazole ointment sent him back to work in two weeks. One month later a large carbuncle appeared on the buttock accompanied by chills, aches and pains. Surgical drainage, supported with sulfathiazole by mouth, again returned him to work in two weeks. Eleven days after this chills and fever with more general aches and pains brought him to the hospital. Next day signs of spotty consolidation appeared, giving the impression of an interstitial pneumonitis, curiously enough without cough. The white count and the ESR were elevated and the blood culture grew out hemolytic *Staphylococcus aureus* in all flasks.

Heavy dosage of sulfonamides and also penicillin controlled the infection and thirty-five days later he left the hospital cured. After his recovery he was fully aware of what the drugs had done for him and recognized that they had saved his life. "However," he said, "I was terrified all through and even in my delirium I was fighting to get back to fresh air and sunshine. I was ambitious to get well." His morale had been held high throughout.

The next person, who at six and one-half was as tall as a twelve year old, had been born with a perineal hypospadias. Five separate operations had failed to correct this condition. Then, as time passed, other inappropriate growth phenomena appeared. When he was seven, for example, his skeletal age equalled that of a twenty-five year old adult. In addition the child's musculature was precociously massive, hair excessive and voice low-pitched and strong. The penis was as large as that of a full-grown adult but no testicles could be found on physical

examination Analysis of the 24 hour urine showed a 17 ketosteroid excretion of 29.6 mgm. One would normally expect 3 to 4 mgm. in a boy of his age. At operation, an almost complete set of female generative organs were found and removed. Dr. Earle Engle's report on these tissues follows:

"The ovaries with normal stromata resemble those of a prepubertal child. But in the mesovarium there was a mass 4 mm. in diameter which exhibited the structure of adrenal cortex. Throughout the removed tissue numerous rests of adrenal cortex were found. Apparently, there is no evidence of testicular tissue, although some remnants of the Wolffian (mesonephric) duct tubules are present."

In addition to the removal of the pelvic organs a partial corticectomy of a much hypertrophied adrenal gland was done.

The child possessed fair intellect and a certain mature poise but it was perturbed by its genital derangement and by the precocious development of form and exterior aspect, which belied its genetically predetermined sex. It was ill at ease and resented too close inspection.

Finally, the third person, an 18 year old Russian Jewess, was completing her high school course, wherein she had achieved distinguished, although to her, unsatisfactory academic standing, when her menses diminished and her weight fell off. Her greatest weight had been 126 lbs. three years before she entered the hospital. At the time of entry she weighed but 71. On admission she gave a clear history of having been ridiculed by her schoolmates because of her fat body. She had no boy friends and spent all her spare time with her parents. There were no siblings. She was very short, approximately five feet one inch. Her face, broad in its frontal and bizygomatic areas, suddenly seemed to disappear at the chin. Her mandible was so small as to give the impression of the fetal jaw-skull relationship. Moreover, the teeth were diminutive, almost like deciduous ones, and each tooth stood separate from its neighbors. The hands were tiny and resembled those of a 6 or 7 year old child, and there was marked digital hyperextensibility. Her menses had begun at the age of 10 and they were regular until 3 or 4 years later when they gradually diminished and ceased altogether with the onset of weight loss. Constipation also supervened and this she could only combat by drinking 6-8 glasses of water. When her bladder was full she said she could move her bowels. She therefore displayed a tendency to polydipsia and polyuria. Recently an increased growth of hair on

extremities and face appeared. The basal metabolism was -36. There was also a delay in water output. Following the ingestion of 1000 cc she required twice as long to excrete the excess as would the average person. This slow type of excretion is found in patients with anterior lobe pituitary deficiency such as chromophobe adenomata or true Simmonds' disease.

A detailed description of her clinical course would be superfluous here. It is typical, however, and fulfilled all the requirements of anorexia nervosa as laid down by R. F. Escamilla and H. Lissner¹ and by J. H. Sheldon.² Our present purpose, however, is not to discuss the differential diagnosis in the case but rather to point out that in the morphology and physiology there appear definite indications of genetic as well as growth and development faults. These faults are clearly in the system controlled by the pituitary-adreno-gonad assemblage.

DISCUSSION

Every ailing person presents a unique clinical challenge, but these three have been selected to illustrate the biological common denominator which they share.

The first case presents an example of direct collision between an adverse element in the bacterial segment of the man's environment and his own personal immunity. It is of course well known that there are great variations in racial and individual powers of resistance to infection and practitioners have long recognized familial susceptibilities to given types of infectious agents. Observations of this kind point to the probability that genetic factors play an important part in such maladies. This concept is further supported by Webster's³ demonstration of the inheritance of mouse brain susceptibility to encephalitic virus. It is also accepted that prolonged or transient adverse factors may reduce the threshold of resistance. Such commonly known predisposing factors as wet feet and over-fatigue from physical or emotional over-strain may act indirectly upon the immunity panel of man. But I have been unable to find impeccable evidence that symbolic traumata act directly upon this phase.

Our Greek cook could recall no chemical or physical resistance-lowering stimuli which preceded the boils. How much the man's anxiety over the threat to his business contributed to the specific lowering of his immunity mechanism cannot be determined by any definite method.

The suggestion that it did so must remain purely conjectural, but a denial of that possibility is equally without foundation. The major therapeutic plan was to support the man's failing immunity by general measures and to counterattack the staphylococcus with appropriate drugs. The cure in this instance was effected by the use of extraneous chemical agents—sulfonamides and penicillin. These substances grappled directly with an equally alien invader. The battleground, however, was laid within the patient's failing body, although the combatants, namely staphylococcus and drug, were both quite foreign to that structure. The implications in the account of his delirium, however, point obviously to the importance of any therapy which might lift his spirit and fortify his "ambition to get well."

The variety of troubles which the intersex patient has faced and will continue to meet throughout his life can be placed squarely at the door of congenital faults in growth and development. But to the wise physician will fall the task of guiding this biological anomaly toward a plan for the best possible adjustment to life. As is well known, in congenital errors both genetic and intrauterine factors often share the blame. Nowhere, however, is the situation more complicated, and still to a large degree obscure, than in the sphere of sex establishment. Most biologists agree that sex determination is not an absolute phenomenon by any means, but they accept the fact that the x and y chromosome combinations are potent factors in the process. These are the primal determinants of sex. Willier⁴ has shown, for example, that in the 96 hour chick embryo the gonad rudiment (including the Wolffian body) can be transplanted into the chorio-allantoic membrane of a host embryo of either sex without altering the graft's capacity for self-determination. In other words, the indifferent gonad rudiment appears already to be organized as to its sex.

Contemporary students of endocrinology place great emphasis upon hormone control of sex. In the present case the evidence provided by the excessive 17 KS excretion and the hypertrophied adrenal cortex correlates positively with the clinical exaggeration of masculine characters and this notwithstanding the presence of female organs in the pelvis. But the truly remarkable thing about such a paradoxical situation is that the health and life of the individual is not necessarily threatened, only that of posterity. It would seem that so far as the first law of nature, self-preservation, is concerned the male or female character of the gonad

is unimportant. Indeed eunuchs and eunuchoids may live in good health to old age. Furthermore, as Lillie remarks, sex is "not an irreversible predestination but a quantitative over-balance in the direction of one sex or the other." The original sexuality is clearly determined by some interplay between sex chromosomes as well as by cytoplasmic contributions. In each new organism, therefore, the sex is established at the moment of fertilization, long before the appearance of Muller's ducts or Wolffian bodies. Following impregnation there exists a variable period of time during which the gonad type is not manifest. At the end of this time, when the nature of the gonad is declared, the endocrine glands begin to function and exert powerful influences upon the physiology of the maturing individual. As A.E. Severinghaus⁵ writes:

"it has been established beyond question that 'genetic balance' (xx, xy) in the chromosomes of germ cells sets up either a male or female pattern, which under normal circumstances will develop into an individual of specific sexuality. In man the pattern is so delicately balanced that additional factors may stay or change the original course of development. Thus, while sex pattern is determined by genetic balance in the chromosomes, the successful achievement of that pattern is dependent upon proper superimposed influence of hormones."

However, the hormones cannot alone be responsible for their superimposed influence upon the embryo of which they are themselves a part. The same chromosomal stamp which the endocrine cells bear affects all the cells of every tissue in the body. The latter can only respond to the circulating hormones in a manner equally specific as that which marks the secreting cells themselves. Thus, in the case of a genetic male pattern, for example, the production of androgens (17 KS) is presumed to be higher than the estrogens, and the body cells to be appropriately reactive. In females the reverse is expected. In the present instance the genetic plan had evidently been for a female, but unknown faults in development led to great over-production of androgen by the hypertrophied and scattered adrenal cortex. The original design was thereby greatly disturbed.

Possibly the foregoing mechanism determines the important phenomenon known as the androgynous mosaic, maleness within the female and femaleness within the male. The gonads themselves are chiefly concerned with posterity through the production of egg and sperm. The effects of their hormones are to large extent determined by

the nature of the extragenital tissue cells which they bathe

So far as the individual's sense of personal security, or ego identity, is involved, it is essential that the androgyny, or extragenital phase of sex should be clearly appropriate to the genic or primary sex plan. Any diminution in a female's sense of preponderant femininity or any awareness of elevated masculinity may arouse unexplained doubts from which flow multiple apprehensions. Precisely the reverse of this situation occurs in the genically preordained male. In his case even minimal emphasis upon the feminine character may be bitterly resented and confront him with a fear-provoking threat. It is not easy for the average male to accept his genic endowment of feminine characters with equanimity. For, notwithstanding the fact that they may be of value to him in situations where the faculties of intuition, sensitiveness and understanding are required, he is more apt to resort to one of the two other available courses of action, flight or fight. Either the adolescent, gynec-stamped male will retreat to the maternal protectorate, which is often masked as chronic invalidism, or he is driven violently by a compensatory andric urge which may lead to heroic exploits or to alcohol, venery and final frustration. The energy which mobilizes such conduct is gathered from every cell in his body.

Although all these extragenital manifestations of sex exist, the popular term "sex problem" is commonly used to refer to tragedies which color the intimate relationships of men and women. Indeed, psychiatry and psychoanalysis have not especially emphasized the significance of sex biology until Zilboorg's⁶ recent fine review of the subject. It is notable that from the Biblical admonition "Go, and sin no more" down to the Freudian formulations the biological foundations of human sex conduct have been undervalued. And from the Delphic oracle, through the history of Catholicism, to the present era of psychotherapy, people have always been more strongly moved by the mystical dissolution of ailments than by the demonstrable mechanisms of their own natures. Moreover, the psychoanalytic thesis of retardation and arrests has emphasized the concepts of sin and guilt which always grow up like weeds about a shattered totem or taboo. Such crimes subject the miscreant to fear of punishment which is expressed in mental confusion and suffering or in the so-called conversion phenomena observed in the signs and symptoms of bodily disease. But, from the medical biologist's point of view, problems in sex are only those resulting from the twisted inter-

play of heredity and environment on body protoplasm Sex problems in the popular sense, on the other hand, actually turn out to be fear problems And so, fear, that master stimulus to the physiology of self-preservation, promptly mobilizes adrenalin which variously influences each and every tissue cell

In view of the powerful genetic and endocrine forces, which by their faulty expressions establish the biological basis for threats to life and ego, it is difficult to understand how post-natal emotional factors alone can have so great a bearing upon sex-motivated conduct as some have attributed to them On this point one is forced to question the arbitrary position taken by Freud⁷ in his third preface to "Three Contributions to The Theory of Sex" He writes

"Besides its thorough going dependence upon psychoanalytic investigation I must emphasize as a character of this work of mine its intentional independence of biological investigation I have carefully avoided the inclusion of the results of scientific investigation in general sex biology or of particular species of animals in this study of human sexual functions which is made possible by the technique of psychoanalysis"

Freud himself, of course, like any other independent investigator, is not to be criticized because he chose to repudiate the stern discipline of scientific method or that he espoused a speculative and literary approach to the vital responses of living forms He possessed the same kind of personal conviction which has led other great men to change their political or religious beliefs and that is to be respected But in the face of well-established and growing knowledge of biological fact can we physicians who purport to be interested in the ailing man as a total organism, wisely make such a sweeping exclusion of those physical and physiological elements which compose the living presence of the patient? How can the neurotic conduct which is said to arise from infantile sex thoughts and phantasies, as portrayed in dreams and odd behavior, be thoughtfully comprehended unless the genetic, anatomic and physiological substrates of sexuality be properly assessed?

If, for example, it is assumed that emotion arising *de novo* from the penumbra penetrates the entire organism and starts hormone secretion, the protoplasmic reaction thereby provoked in the body cells must still depend to large extent upon the genetic nature and conditioned habits of those very protoplasms Moreover, as has been recognized for many

years and much emphasized by Adler⁸ and other psychoanalysts, the threat to security, based on an inner sense of corporal incompleteness or inadequacy, is the parent of fear. Consequently a clear understanding of the patient's biological faults may help the physician to comprehend that fear and allay it through an educational form of therapy. But in addition, certain symptoms which arise from lesser maladjustments in the androgyny can often be helped by appropriate use of hormones.

The very name anorexia nervosa at once implies that the major cause of the young Russian girl's sickness is "purely" psychological. Moreover, the psychiatrist's note in her chart states that "from the psychiatric point of view this is a very typical case of anorexia nervosa." But, because of the obvious faults in the patient's physical growth and development, there is much to be said for a physical and physiological origin of the malady. Indeed, those stigmata are so emphatic and so often seen in other similarly afflicted persons that one is justified in saying that this individual is a typical representative of those persons who may express their inadequacy in this strange disease picture. Though her 17 KS excretion of 10.3 mgm for 24 hours is within normal limits there are morphological indications of more than average emphasis upon the andric component. These are to be seen in the heavy bones and big joints, the wide shoulders, the contours of the thighs and legs and the distribution of muscle tissue which became visible as fat disappeared. More noticeable, perhaps, and more consciously appreciated by the patient herself, was the loss of menstrual function and the increase in hair which grew in andric patterns. As was mentioned in the preceding discussion, the concept of inappropriate or incomplete sex differentiation constituted a basic threat to ego security. The starting point of the girl's difficulty may well have been the deep inner confusion produced by the congenitally distorted sexuality. The overemphasis upon her andric component was only sufficient to stimulate but not to satisfy what psychoanalysis has termed the "masculine protest." It is interesting in this connection that perhaps the first symptom was the disappearance of menstruation. From then the neurosis developed increasingly. Her ostensible reason for reducing her diet was the fear of being ridiculed as obese. This rationalization was re-enforced by her lack of masculine admirers. But the genetic stamp and the subsequent growth and development asymmetries had prepared the way. All of the reported characteristics which are in the zone of the pituitary-

adreno-gonad control are obviously the product of her chromosomes in collaboration with the intrauterine and post-natal environment. In this patient they show a strong andric trend. When these chromosomal foundations are very skew, one can expect vital functions to deviate from normal to an increasing degree as the pressure of life increases with age.

The stories of these three sick people hold a deep significance for us. They illustrate that beneath each clinical syndrome there is a complex common denominator composed of human protoplasms and their sharply individualized expressions. Underneath them all lie the protoplasmic factors which were originally brought up from the sea. Some of these ancient characters, shared by every animal species which has existed, are now demonstrable. Recently Schmitt, Hall and Jakus⁹ have shown by means of the electron microscope that collagen fibrils of identical structure are found in a variety of living forms and of some living fossils, such, for example, in reverse order of remoteness, as mammals, amphibians and mollusks. New and divergent mechanisms which developed in response to new demands of environment have resulted in the differentiation of the species, and then, within the species, of individuals. The latter likewise display great diversity not only between total personalities but even in the cell type pattern which each man's leukocytes develop in vital cultures of the buffy coat of his blood.¹⁰ These recent findings reflect Landsteiner's¹¹ vision and later demonstration that different individualities could be recognized in the cellular and chemical nature of the blood itself. And this fact Landsteiner believed was a parallel phenomenon to the specificity of tissue transplants which has long been known to surgeons and recently so well demonstrated by Leo Loeb.¹²

The chromosomes of our germ cells contain all these ancient and recent characters which dominate the descendent individuals and their separate parts. Then, through some accident of breeding or nurture, the established balances are disturbed and the resulting imperfect creatures are cast upon the world. In their effort at adjustment the vital reactions of these inadequate individuals become the signs and symptoms of disease which drive them to us for relief. Being physicians we are obliged to deal with them as best we may, according to the established laws of nature.

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A CRITIQUE OF PSYCHOTHERAPY IN ARTERIAL HYPERTENSION*

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IN considering the complicated subject of arterial hypertension it is appropriate at this time to review the experiences with psychotherapy. Both in this approach and in others there is admittedly a great deal that we do not yet know. Professor George Santayana used to talk about defining the limits of our ignorance. What are these limits?

We do not know, for example, whether the process is a reversible one, whether the impulses which give rise to arteriolar constriction are humoral or neural in origin, or both. In spite of the brilliant researches of Goldblatt¹ and others, we do not know what part the kidneys and the renal circulation play in bringing it about. Indeed, it would be hard for us to define this disease further than to say that it represents a morbid state in which elevation of the systolic and diastolic blood pressures—either fluctuating or constant—occur in association with arteriolar vasoconstriction. We do not know why the life expectancy of some is unaffected while others succumb quickly to the malignant form.

Once we thought that hypertension was associated with a certain bodily habitus—that it was more prone to exist among the short and the squat and the red-faced. Those of you who have occasion to see patients suffering from this disturbance have found them to be lean and spare, tall and pale-faced as well. According to Page,² “an accurate correlation of body build, height and surface area with arterial pressure cannot be established.” Again citing Page as my authority, and contrary to generally accepted beliefs, there is no sufficiently documented testimony to support the view that heredity plays a vital part in the genesis of hypertension. He cautions against ascribing too great importance to heredity and suggests that this aspect of the problem needs reinvestigation on a more comprehensive basis.

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This then is part of the staked-out claim of our ignorance. To outline it is not to underestimate the importance of recent researches and their contribution to our understanding of the physiological mechanisms of this disorder.

That it has still another aspect is now rather generally accepted. In this terrain our ignorance is even wider and more varied. It would be a challenge, indeed, to plumb its depths and to chart its perimeter. I am speaking now, of course, of the psychological aspects of arterial hypertension which some have attempted to explore. Alexander,³ Menninger,⁴ Moschowitz,⁵ Rennie,⁶ Saul⁷ and Weiss⁸ among others. In collaboration with Nathan Ackerman,⁹ I have myself put in four years at hard labor breaking ground. I cannot say that we struck gold, but I hope at least that we uncovered some facts. These are to be published in a much over-due monograph of which the page proof has finally come through. The work was supported by a grant from the Josiah Macy, Jr. Foundation and was done in cooperation with Drs. Cohn, Schroeder and Steele of the Hospital of the Rockefeller Institute. The investigation was based on the clinical and psychiatric study of 24 patients suffering from arterial hypertension.

I should like to say here in parenthesis that the description of the personalities of these patients which I shall presently offer and which derives from our own work and, in part, from that of others does not, in all probability, apply uniquely or exclusively to the hypertensive state, though none of our patients differed widely from it. I have, myself, yet to be convinced that characterological studies made by those interested in psychosomatic medicine have any specific etiological significance. Not beauty alone but artefacts as well may dwell in the eye of the beholder.

The facts that appear from our own studies and from others' are these. Sufferers from arterial hypertension exhibit a disorder of personality which has been conveniently described by the term "neurotic." This disorder manifests itself in their inter-personal relationships, in their sexual adjustments and often in their occupational achievements. They are characteristically tense individuals given to states of anxiety and depression. Much of their emotional tension can be ascribed to inhibited, but not deeply repressed, aggressive impulses. It is often possible to trace the history of this neurotic development of character to early childhood when the common feature is an extreme degree of

insecurity, with a greatly unsatisfied dependent relationship to a threatening parent. Given this bad start the patient then falters through life—unable to relax, unable to enter into secure and satisfying relationships, always on the defensive, ready to fight but afraid to fight.

With this precarious adjustment the apple-cart of the patient's emotions is easily upset. The death of a parent, or partner, a motor accident, the illness of a child, business reverses—almost any event which jeopardizes his security—which is felt either directly or by implication as a threat to his life—increases to an intolerable degree the quantum of his anxiety and of his reactive depression. In our series of cases it was observed that the clinical discovery of elevated blood pressure frequently coincided with such a traumatic experience.

I do not wish to be understood as stating that this disturbance of character or its ultimate outcome is the cause of hypertension. It is, on the contrary, my suspicion that the psychological disorder and the physiological disorder each represents a different aspect of a more basic disturbance, the nature and cause of which is unknown—though its existence is often foreshadowed early in life.

What therapeutic implications are to be drawn from these observed facts and from this theoretical interpretation of them? The first is that psychotherapy cannot be directed at blood vessels. It can be directed at the emotions. Its aim is to treat the person, not the vaso-constrictor mechanism. This must be kept clearly in mind. What we can accomplish will depend—as in any other therapeutic procedure—not only upon our skill, but also upon the material with which we are forced to deal. It is not a plastic, easily workable one. These patients have usually extraordinarily rigid personalities. Their aggressions are fixed, they are not fluid or readily mobilizable. If they were, they themselves would have spontaneously found a more satisfactory and less destructive expression for them. Much of their anxiety is absorbed in their symptoms. It is not easily dislodged and when it is it may sweep over them and produce a state bordering on panic. The underlying depression is constantly being fed by the conviction that they are sufferers from a fell malady, that fate has dealt them a body blow. Each symptom winds up the main spring of their tension, increases their anxiety and undoubtedly reflects itself in their vascular apparatus. Deep psychotherapy in this illness is, therefore, no task for the bungler or the amateur. It is as dangerous, as delicate and as difficult as surgery.

Like the surgeon the psychotherapist must know something of the topographical anatomy of his patient. His aims are to restore a more normal functioning of the emotions. Persuasion and reassurance, though important tools, are seldom sufficient. They will not remove tough bands of connective tissue and they will seldom remove the strictures and inhibitions against which these patients live their unfulfilled lives.

Again like surgery, the choice of procedure will depend not upon pre-conceived doctrinaire generalizations but upon careful clinical observation. It is as absurd to say that every patient suffering from hypertension should undergo psychoanalysis as it is to say that every case of neoplastic disease should be operated upon. The decision is based first of all on the patient's ability to stand operation, secondly upon the nature of the lesion and its accessibility, and thirdly upon the prospects for a successful result. Surgeons no longer operate because there is nothing else to do, but rather for specific reasons empirically derived. In the domain of psychiatry and psychoanalysis the same critical standards are now happily being invoked.

The surgeons have, to be sure, a great advantage over us, not only is their handiwork more precise, but their results are referable to a statistic which it would be folly to assert that we possess. We have none.

Lacking a statistic we can at best proceed according to certain rational principles. I have stated what they are. The problem is that of treating a severe character neurosis in which anxiety, depression and suppressed aggression are the cardinal psychopathological features. The method of choice will vary from cheerful neglect (based on that much vaunted common sense which we are all supposed to possess in such good measure) to deep psychological exploration. The latter you will grant is a matter for the expert. What is to be hoped from it we cannot say. There is as yet no evidence that psychoanalysis or any other psychotherapeutic procedure can reverse the physiological process or change the destiny of this disease—be it benign or malignant. The problem is an open one. It needs further investigation. The ground has now been cleared for such an undertaking. It is probable that we can do more by way of prevention than cure.

There is evidence that a correlation exists between levels of pressure and emotional disturbance and that suitable psychotherapy can ameliorate some symptoms such as headache, fatigue, palpitation, dizziness, shortness of breath and the fear which these engender.

We have observed this ourselves and so have others Weiss¹⁰ has stated for example "For some time now I have felt and taught that essential hypertension cannot be eradicated by any psychotherapeutic process but that almost every patient can be benefitted by psychotherapy" In a review⁸ of the records of 200 consecutive patients with symptoms of hypertension he selected 144 which "seemed to correspond to the clinical picture of so-called essential hypertension" (note the cautious conservatism of his words) Ninety-three of these lent themselves to satisfactory psychosomatic investigation and in only seven did he conclude that psychic factors bore no relationship either to the onset of hypertension or to the production of symptoms Case I of his series shows a quite remarkable coincidence between periods of elevated blood pressure and vaso-spastic retinitis with anxiety producing episodes and with what Weiss calls periods of "throttled aggression"

In Alexander's³ carefully studied psychoanalytic material he presents blood pressure readings of 161/110 when his patient was emotionally disturbed as compared with 142/98 when calm Saul⁷ has made similar observations of fluctuations of blood pressure with mood and, more especially, with variations in the intensity of the so-called transference situation It must be borne in mind that fluctuations may occur spontaneously without reference to known therapeutic effects

The most striking, unique and dramatic case in the literature is a patient of Lewis B Hill,¹¹ who recalled early in the course of psychoanalytic treatment a deeply suppressed childhood memory This was brought up with intense effect The patient exhibited an extraordinary degree of rage and guilt over a childhood experience in which his mother struck him with a pony whip The recall and reliving of this traumatic episode was followed by a critical sustained and enduring fall of both systolic and diastolic pressures Perhaps this single observation is a prototype of others to come But, in honesty, it must be said that from a clinical and physiological point of view the case is insufficiently documented and the diagnosis remains open to question

Leaving now out of consideration all efforts at deeper psychodynamic inquiry and turning to the every day handling of these patients, I believe that our new knowledge can be put to effective use We are dealing with tender vessels They need to be protected from emotional strain, especially from demands upon a self-reliance they do not possess There is no good in telling them to "buck up" and "forget

it." They need the maximum of reassurance about the disease itself. They need very much to feel that some one person is watching over them and will take on his shoulders the burdens of their worries. They need to be encouraged to express their aggression, not by hurling dishes or epithets at their wives, but by directed work and play and by physical exercise, if this is compatible with their cardiac reserve. They need to be weaned away from an over-concern with the level of their blood pressure. The experienced doctor will vary his methods. With some he will be frank, with others he will be silent and to some he will have to dissemble. The manner in which this frightening fact is first presented to them is of the utmost significance. If the doctor shows his own alarm when the mercury column tops 220 it is likely to be communicated at once to his patients.

It is well to remember that almost all our therapy is in essence psychotherapy. Drugs and sedatives, rest and exercise, diet and baths all have psychotherapeutic implications, and this is just as true of surgery. The surgical amphitheatre has become the court of last resort in this illness. Perhaps in time we will learn on what findings nature bases her verdict—why some patients respond to sympathectomy with a reduction in blood pressure, a recession of retinitis and a merciful relief from headache, while others do not. I hope that it will not be thought too "tender-minded" of me if I suggest that the attitude which patients bring to the ordeal of operation may in some measure determine its effect upon them. For there are those who face it as they would doom and there are others who look upon it as a deliverance.

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TRICHINOSIS A MAJOR HEALTH PROBLEM IN THE UNITED STATES WHAT SHALL BE DONE ABOUT IT?^{1 2}

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HISTORICAL

TRICHINOSIS is a disease which probably dates back to antiquity. It is believed to have been responsible for the Mosaic law which prohibited the Israelites from eating the flesh of the pig. The parasite, however, was not discovered until 1835. In that year, James Paget, then only 21, and a first-year medical student at St. Bartholomew's Hospital in London, encountered in the muscles of a human subject in the dissecting room, minute whitish spots, which when examined under the microscope were found to be cysts, each enclosing one or more little worms. The cysts were further studied by Richard Owen, who named the parasite *Trichina spiralis*. The present name, *Trichinella spiralis*, was given to the worm by Railliet in 1896. The trichina was first found in the meat of the hog in 1846 by Joseph Leidy, a Philadelphia physician and naturalist. Leidy noticed minute whitish specks in a slice of pork which he was eating. These specks struck him as being similar to trichina spots which he had seen in the muscles of a human subject at autopsy only several days previously. He examined the remainder of the meat microscopically and found it full of trichinae.

The ability of the worm to produce disease in man was first recognized in 1860 when Friedrich von Zenker, a pathologist in Dresden, Germany, discovered the life cycle of the parasite. In that year, a 20-year-old servant girl, diagnosed as having typhoid fever, was brought into a hospital and died about thirty-three days after the onset of her illness. Zenker examined muscular tissue taken from the arm of the patient at autopsy for degenerative changes characteristic of typhoid fever but instead was startled to find numerous trichinae which exhibited obvious signs of life. Zenker's further investigations with regard

¹ Read before The Society of Medical Jurisprudence of New York, May 14, 1945

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to this case sound like a modern detective story. He found larval worms in all the skeletal muscles and mature adult worms in the intestines of the patient. Zenker visited the household in which the servant girl worked and found trichina larvae in the ham and sausage that was prepared from a pig that had been slaughtered 4 days prior to the onset of the girl's illness. In addition, all the members of the household, who had eaten of the meat of this pig, had fallen ill. He concluded that the entire cycle of development of this parasite could take place in one host and that the trichina larvae were probably disseminated through the body by way of the lymphatics and blood stream. These conclusions are now known to be correct.

Soon after Zenker's discovery there occurred in Germany two notable epidemics. In the first epidemic which occurred in 1863 in Hettstadt, a town with a population of 4,000, 158 persons fell ill, of whom twenty-seven died, a mortality rate of 17 per cent. In the second epidemic which occurred two years later in Hedersleben, a town with a population of 2100, 337 persons fell ill with trichinosis, of whom 101 died, a mortality rate of 30 per cent. These two epidemics brought forcibly to the attention of the medical profession of Germany the great danger of eating uncooked pork. As a consequence there was soon instituted in many parts of Germany a compulsory system of microscopic inspection of pork, and the meat of every animal found to be trichinous was destroyed. Similar systems of inspection of pork have been in force in other countries of the world, including Sweden, France, Argentina, and Chile. Between the years 1891 and 1906 the United States Department of Agriculture was authorized by act of Congress to inspect all pork which was intended for export since American pork had largely been excluded from European markets on account of its frequent infection with trichinae. The Act of Congress authorizing microscopic examination of pork did not however achieve its purpose and such inspection in the United States therefore was discontinued in 1906. The label, "U S Inspected and Passed" on pork has no reference whatever to the presence or absence of trichinae, since non-processed pork bearing this label may contain living trichinae. The Federal Government does not examine pork microscopically.

METHOD OF INFECTION

Man acquires the infection almost exclusively from the ingestion of

pork containing viable trichinae. The pig acquires the infection primarily from the consumption of bits of raw trichinous pork in uncooked garbage. The meat fibers and the walls of the trichina cysts are digested in the stomach of the host, liberating the living trichina larvae which develop within a few days into sexually mature adult forms in the small intestine. Beginning at the end of the first week of infection and continuing for a number of weeks thereafter, the gravid females, imbedded in the mucosa of the bowel, deposit their living larvae into the mucosa, whence they enter the lymphatics and then the blood stream, traverse the capillaries of the lungs to reach the left side of the heart and are then thrown into the general systemic circulation whence they finally enter the striated muscle fibers. At the time of birth, the larvae measure approximately 100 microns in length and 6 microns in diameter, the diameter therefore being somewhat less than that of a red blood cell.

SYMPTOMS

Within the skeletal muscles the larvae enlarge and set up an inflammation which is responsible for many of the symptoms of the disease. At 17 days after infection, the larva begins to coil and at about thirty-five days after infection, it reaches its maximum growth and then begins to encyst within the muscle fiber which has undergone degeneration. The degeneration of the muscle is attended by considerable inflammation and edema and in heavy infections the inflammation and edema may be so marked as to give rise to violent symptoms. In such severe infections, trichinosis may truly be a "terrible" disease. Indeed, movement may be so painful that the patient may lie in one position constantly for days, afraid even to move his eyes or his tongue, to speak, or even to swallow. The heart is regularly invaded by the parasite and an inflammation is set up within the myocardium. In moderately severe or in heavy infections, the myocarditis may be dangerous since it may cause sudden death or may lead to heart failure. After some weeks, depending upon the severity of the disease, the inflammation in the heart, as in other striated muscles, subsides. Within the skeletal muscles, the parasite if not destroyed, becomes well encapsulated and may remain viable for many years. Within the heart, however, the parasite is regularly destroyed even though it has set up a severe inflammation. Encystment of *Trichinella spiralis* within the myocardium never occurs. An-

other danger of trichinosis is that which results from capillary damage and petechial hemorrhages within the brain. Encephalitis and meningitis sometimes are found in acute fatal cases. The *incubation period* varies from two to twenty-eight days with an average of ten days. The disease has been divided into the following stages: (a) intestinal, (b) invasive, and (c) convalescent. Most of the symptoms are due to the effects of invasion of the newly-born larval parasites. Particular mention may be made of supraorbital edema and fever, of the diagnostic sign of eosinophilia, and of electrocardiographic evidence of myocarditis.

DIAGNOSIS

Eosinophilia is the most important single diagnostic sign in trichinosis. It begins to appear as early as the tenth day, and reaches its peak during the third week of infection. There are several other laboratory tests of diagnostic value. An immediate type of allergic response may be obtained following the intradermal injection of a trichina antigen in a dilution of 1:7000 or 1:10,000. This "immediate intradermal reaction" may be elicited on and after the 17th day following infection. Specific blood precipitins and complement-fixing antibodies may be found on and after the 28th day of infection. The demonstration of larvae within the blood, cerebrospinal fluid, or the skeletal muscle of the host is of prime importance in establishing the diagnosis. Trichinae may likewise be demonstrated in portions of uneaten suspected meat. In the examination of muscle from the patient during life, the following methods may be used to detect trichina larvae: 1) microscopic examination of fresh muscle within a compressor or "trichinoscope", 2) maceration of muscle to detect young larvae which have not yet attained their full growth, 3) digestion of muscle tissue of the patient at 37° C for eight to 12 hours, using a digesting fluid which consists of 1 per cent hydrochloric acid and 1 per cent pepsin, and 4) biopsy. Serial microscopic sections should be made if necessary of the tissue taken for biopsy. The diagnosis of trichinosis is often not easy and is frequently missed since the symptoms may simulate those of numerous other diseases. When the correct diagnosis is suspected, appropriate methods of examination will usually enable one to demonstrate the existence of the parasite.

TREATMENT AND PREVENTION

Treatment is largely symptomatic. Bed-rest should be prescribed

until all danger of heart failure or of complications has passed. There is no specific remedy except that of prevention. At the present time, prevention is largely up to the ultimate purchaser or consumer of pork and consists principally in thorough cooking or sufficient heating of the pork and pork products. The Federal government recommends that pork should be boiled at least thirty minutes for each kilogram of weight (2 2 lb). Another approximate guide for thick cuts of ham or pork is to cook them one-half hour per pound. All portions of cooked pork should be white. *Trichinae* may also be killed within pork by methods of freezing. In order to destroy by freezing living trichinae within cuts of meat not exceeding six inches in thickness, governmental regulations require that a temperature of not less than 5° F be maintained for at least 20 days. Incidentally, this temperature is within the range of deep-freeze cabinets, such as are used in the home.

INCIDENCE OF TRICHINOSIS IN UNITED STATES

In 1932, the meat of 14 million hogs was subjected to microscopic examination in Prussia and trichinae were found in only 0.001 per cent of the animals or in 9 hogs per million. In 1933, the meat of 14 million hogs was similarly examined and only 0.0008 per cent or eight animals per million were found trichinous. During the years 1898 to 1906, the meat of 8 million hogs was microscopically examined in the United States and 1.41 per cent, or over 14,000 hogs per million, were found trichinous. The average incidence of trichinosis among hogs in the United States at present is as follows: 0.4 per cent of hogs which are fed cooked garbage, 0.8 per cent of hogs fed grain, 6.4 per cent of pigs fed uncooked garbage and 15 per cent of animals fed slaughter-house offal. A conservative estimate of the average incidence of trichinosis among hogs in the United States at the present time is 1.5 per cent. Each year about 90 million hogs are slaughtered in this country. If 1.5 per cent of these are trichinous, and if each hog furnishes meat for about 100 meals, there will be consumed within the United States each year 135 million meals of pork containing trichinae. Fortunately, of course, in most instances the trichinae will have been killed. Too often, however, live trichinae will be ingested and it is no wonder, therefore, that in recent surveys of autopsies in the United States, an average of 16 per cent of the population should have been found to harbor trichinae. This figure is low, for when more thorough investigations are made,

the incidence at autopsy has been found to be as high as 36 per cent. It would be a conservative estimate to state that approximately 25 per cent of the general population of this country develop trichinous infection during their life-time. In other words approximately one person in every four becomes infected with this parasite. Fortunately the infection is subclinical in the majority of cases. It is estimated that at least 5 per cent of those who become infected show signs of illness but that only about 1 per cent of all who are infected become sufficiently ill to confine them to bed with clinical trichinosis. The mortality rate from clinical trichinosis in the United States is 5 to 6 per cent. It has been said that "trichinosis is one of the major health problems in the United States" and that "the United States has the greatest problem of trichinosis of any country in the world." At the present time, the public is not sufficiently protected against the dangers of this disease.

MEDICO-LEGAL ASPECTS

From the medico-legal standpoint, the manufacturer or packer warrants to the public generally that the food which he produces is fit for human consumption. If the consumer becomes ill with trichinosis, the manufacturer or packer of the trichinous pork may be held liable because of his negligence in the preparation of the food or because of breach of the implied warranty of wholesomeness and fitness of food which is sold for human consumption. The majority of claims have been based upon the breach of implied warranty and in most instances judgment has been rendered for the plaintiff.

CONTROL MEASURES

Since pork is a desirable food, being rich in protein and fat and very rich in vitamin B₁ (thiamine chloride), is usually easily digested, is savory and nutritious, is it not amazing that the public should have to consume it so often at the risk of health and life? The danger of trichinosis appears to be particularly great in the case of sausage made with pork which is raw or insufficiently cooked or under-processed. The situation today in regard to the control of trichinosis may be likened to that which prevailed in the dairy industry of this country thirty or more years ago, prior to the general adoption of pasteurization of milk. Certainly no one will now argue the value of effective pasteurization to the public as well as to the dairy industry. For similar reasons, methods

which are known to be effective in the destruction of living trichinae in pork and which do not produce injury to the quality of meat should be adopted throughout the United States at the earliest possible moment. The costs of instituting measures which will safeguard the health of the public must of course be borne eventually by the consumer but, as in the case of pasteurized milk, the consumer will be glad to pay this small extra cost in order to have the added measure of protection. Incidentally, such protection must inevitably lead to a greater salability of pork products and a greater willingness on the part of the public to consume pork. The adoption of such protective measures by the packing industry will be found to constitute good business practice.

Granted that some method should be adopted for the protection of the health of the public, let us consider what methods of controlling trichinosis are available and practical. In general there are three available methods of control, as follows: 1) microscopic inspection of meat from every slaughtered hog, 2) cooking of all garbage that is to be fed hogs, and 3) processing of all pork to render it free from viable trichinae.

1 *Microscopic inspection of pork* Microscopic inspection of pork requires that one or more specimens of muscle from every slaughtered hog shall be examined under the microscope for the presence of parasites. The arguments that this method is too expensive and too time-consuming for present-day high-speed American needs are ridiculous. No expense is too great as far as the health of the public is concerned. Furthermore, there are rapid methods of examination, such as the "phototrichinoscope." Additional time-saving methods would no doubt be devised if necessary. Other countries have found microscopic inspection practical and the method has been in vogue in Germany, France, Sweden, Argentina and Chile, in most instances for many years. The Act of Congress which, beginning in 1891, authorized the inspection of all pork which was intended for export, was repealed in 1906, principally because the German government did not accept the certification of the U. S. Department of Agriculture that the pork bearing its label was free from trichinae. The chief valid objections to the inspection of pork are: 1) there is a large human error in the microscopic inspection, 2) trichinae may not be found in the particular specimen of muscle examined, and yet be abundantly present in other muscles, and 3) the public may acquire a false sense of security in

eating pork raw, since it has passed microscopic inspection Thornbury, in 1897, failed to find trichinae in the diaphragm of approximately 24 per cent of 1043 trichinous hogs in which parasites were found in one or more of three muscles examined It is principally the diaphragm from which specimens are generally taken in the microscopic inspection of pork

2 *Feeding of cooked garbage to hogs* The feeding of cooked garbage to hogs would be an effective method of control if it could be universally enforced Such enforcement appears to be possible in the case of large growers of swine, but it would be practically impossible to control small producers of pork and farmers who raise small numbers of swine This method of control is considered to be the least practical of the methods which have been advocated

3 *Processing of pork* Under the term "processing" are included methods of refrigeration, cooking, smoking, salting, and any other means which may be employed if carried out according to regulations set forth by the U S Bureau of Animal Industry for methods which are effective in destroying viable trichinae within pork and pork products At the present time the only pork products which are reliably free from living trichinae are those which are manufactured in plants operating under governmental supervision, the products being processed according to Federal specifications so that they may be eaten without further cooking If the Federal government would require that *all* pork and pork products which are shipped in interstate commerce shall be so processed as to render the meat free from viable trichinae, and if local and state health authorities would adopt similar regulations for pork which is sold locally or within the state, and if in addition, the Federal government and/or the local and state health authorities would require that all pork offered for sale bear the label "This product conforms to Federal and/or local or State regulations for processing of pork", we would then have an effective method of control of trichinosis Such a method would obviate the dangers present in microscopic inspection and the weaknesses which are inherent in laws that require that only garbage which is cooked may be fed to hogs The responsibility for the proper manufacture of pork and for guaranteeing the wholesomeness of the pork as a food would then be placed precisely where that responsibility belongs, namely, upon the manufacturer or packer The loopholes in such a method of control would be few in-

deed and the protection which would be afforded to the public would be adequate. In short, the pork supply would be safe for human consumption.

We believe that the most practical method of control of trichinosis in the United States is the method of processing all pork. It remains for the public to insist that its health be adequately safeguarded against the danger of acquiring trichinosis in the pork which it consumes. There is no question but that sooner or later the public will demand such protection.

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THE VALUE OF PROTEIN AND
ITS CHEMICAL COMPONENTS
(AMINO ACIDS) IN SURGICAL REPAIR *

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THE role of protein nutrition in repair may be discussed under three headings 1) wound healing, 2) maintenance of tissue integrity, and 3) convalescence I shall discuss the first two topics briefly, take up the subjects of the loss of nitrogen in disease, the consequences of protein loss to the body, and the inadequacy of natural food to replenish this loss Then I shall discuss our studies on convalescence, presenting our work in five categories Finally, I shall discuss the role of hydrolysates and amino acid mixtures in clinical nutrition

Wound Healing The older work by Clark¹ and Howes² on wound healing was brought closer to the clinic by the series of studies by

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The work described in this paper was initiated under a grant from Mead Johnson and Company and is being continued under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York University It was the product of the work of a team consisting of Drs Arthur Mullin Wright, J H Mulholland (now Lt Col MC AUS), Irving Barcham George R Gerst and many members of the Surgical Staff of New York University College of Medicine and the New York University Surgical Division of Bellevue Hospital, as well as of Lilly Schmidt and her staff of chemists and Mary Coughlin and her nursing staff

Ravdin and his associates^{3, 4, 5, 6} on the relation between wound dehiscence and hypoproteinemia in dogs. These authors attributed wound disruption to two factors, edema and incapacity to form fibroblasts as a result of the lack of building material. Whipple⁷ in 1940 in his presidential address before the American Surgical Society laid special emphasis on the relation between the lag period of wound healing and protein nutrition, and it is now the consensus of well-informed surgical opinion that protein deficiency plays an important role in wound dehiscence.

Tissue Integrity The role of protein nutrition in the maintenance of tissue integrity was suggested by our observations on non-neurologic cases of bed sores.⁸ In this study a close association was found between the occurrence of bed sores and the plasma protein level, all patients with bed sores having levels mostly below 5.5 grams per cent and never over 6.35, and a negative nitrogen balance. When the nitrogen balance was reversed from negative to positive, the bed sores healed promptly. This finding led to the formulation of the hypothesis that bed sores are pressure sores occurring in tissues which, as a result of being devitalized by protein deficiency, undergo pressure necrosis more readily than normal tissues. It must be mentioned that bed sores do not occur in cases of nephrosis, even with a plasma protein level of 3.5 grams per cent. It is possible that tissue edema, by more equally distributing the pressure, prevents this.

Production of Protein Deficiency How is protein deficiency produced? In experimental animals it can be produced by a protein-poor diet, by plasmaphoresis, or by a combination of both.^{9, 10} Clinically, similar mechanisms are operative and in addition, a third one, namely, increased metabolic loss of nitrogen as a result of injury or disease. The combination of decreased intake and increased output can deplete the protein stores in a few days.

Decreased intake may be caused by poor appetite, and it may here be said that appetite, while a good guide to nutrition in health, is a poor guide in disease. The occurrence of actual nausea, vomiting and pain also decreases intake. Then there may be poor absorption from the gastrointestinal tract as a result of diarrhea, of hyperperistalsis or of a diseased mucosa. Poor intake may also be due to neglect on the part of the attendants, that is, a physician may not prescribe an adequate diet or fail to watch the patient's nutritive status. Many surgeons have de-

TABLE I

NITROGEN CONTENT OF HOSPITAL WARD DIET	
	<i>Total nitrogen, gram</i>
Wednesday	6.245
Thursday	14.827
Friday	8.189
Saturday	5.211
Sunday	8.6846
Monday	10.938
Tuesday	12.484
<hr/>	
Total Nitrogen for week	65.94
Average Nitrogen per day	9.42

veloped an over-dependence on blood transfusions, expecting an occasional blood transfusion to supply a patient's caloric and nitrogen requirements for a week. Lastly, the hospital diet may be sub-standard. Charity hospitals are the greatest offenders in this respect. Table I shows the nitrogen contents of the basic diet of a charity hospital for a period of a week. This basic diet was based on Sherman's recommendation¹¹ for healthy individuals but has been adopted indiscriminately generally by hospitals as an adequate basic diet also for hospital patients. It will be seen that on most days the intake falls below the prescribed minimum and that the average is in the neighborhood of 9.5 grams of nitrogen per day.

Increased Metabolic Loss. The average nitrogen loss in the urine of a healthy adult is about 13.5 grams nitrogen per day.¹² This amount goes down in starvation. During disease it may go up to two or sometimes three times this figure, as found by Cuthbertson¹³ and confirmed by a number of other workers, prominently among them Browne,¹⁴ Albright¹⁵ and Howard.¹⁶ This increased loss has been attributed to a number of factors, among them injury and autolysis of tissues and to an endocrine factor supposed to be elaborated by the cortex of the adrenal gland. This increased loss has sometimes been called "toxic loss of nitrogen" or "catabolic loss." Whether the nitrogen lost is all replaceable has been a moot point, some workers think this can be accomplished, while others do not. As a result of recent work, it seems that the con-

TABLE II

CASES OF BURNS RE-ARRANGED ACCORDING TO PERCENTAGE OF
BODY SURFACE INVOLVED

<i>Name</i>	<i>Body Surface Burned %</i>	<i>Age of Burns Days</i>	<i>Nitrogen Loss Grams Per diem</i>
F W (1)	8	40	4 07
F W (2)	10	8	1 58
J Mc	15	21	2 98
J W	15	23	7 65
J S	15	4	1 79
A B	20	2	1 5
J Mc(1)	21	15	3 56
J Mc(2)	30	6	5 15
M W	40	94	6 45+
A F	50	4	9 07+

ditions in which this loss has been thought irreplaceable have been narrowed down. The question still remains. In what disease states and under what conditions is this metabolic loss replaceable?

Loss in Exudates Another avenue of loss of nitrogen is in exudates and other body discharges.¹⁷ This is comparable to plasmaphoresis in experimental animals. Table II shows the amount of nitrogen lost per twenty-four hours in cases of burns. It will be seen that A F., with 50 per cent surface involved in burns, lost at least 9 grams of nitrogen per day (some leakage having occurred into the beddings). This represents about 55 grams of protein or about one-third of the amount present in the blood. Were it all to come acutely from the blood, this amount of loss alone would have led almost to the development of shock.

Table III shows the amount of nitrogen lost in the exudates of different surgical conditions. S S had an avulsion of the perineum and back, covering about 15 per cent of body surface. Three months after his injury he was still exuding 6.37 grams of nitrogen in twenty-four hours, which is equivalent to 664 cc of plasma. R W was a case of radical mastectomy who lost 4.26 grams of nitrogen in the first twenty-four hours, dwindling down to 1.2 grams in three days. A G, who had an abdomino-perineal resection for carcinoma of the rectum, lost 6.22 grams of nitrogen in the first twenty-four hours. This loss had decreased

TABLE III

NITROGEN LOSS IN DIFFERENT EXUDATIVE SURGICAL CONDITIONS

Name	Diagnosis	Date of Injury or Operation	Date Collect	Total N Exuded 24 hrs, gm	Eqv in Proteins gm	Eqv in Plasma cc
S S	Avulsion Perineum and Back	7/7	10/23	6.87	39.81	664
R W	Radical Mastectomy	10/25	10/26 10/30	4.26 1.2	26.65 7.50	445 125
A G	Abd-Perineal Resection (Cancer-rect)	8/18	8/14 8/16	6.22 2.07	38.87 12.97	644 216
O Mc.	Abd-Perineal Resection (Infected Cancer-rect)	8/9	8/18 8/21	6.97 3.47	42.46 21.69	707 723
F C	Lung Abscess Pyothorax		4/24	9.57—	59.8—	996
A C	Empyema			9.37	58.56	976
H L.	Liver Abscess (5 cm. diam.)	12/26	12/28	1.98	12.63	210

to 2.07 in twenty-four hours. Both of these cases suggest an effort on the part of the body to seal off exuding surfaces. O Mc. was a case of abdomino-perineal resection which was infected. The loss in the pus nine days after operation was 6.9 grams but within three days after drainage was instituted, it had decreased to 3.47 grams. F C and A C were, respectively, cases of lung abscess with pyothorax and of empyema. They lost respectively 9.57+ and 9.37+ grams, equivalent to almost 1,000 cc of plasma or about one-third of the amount of circulating protein in the blood. This magnitude of loss may in part account for the emaciation and high mortality observed in this type of case. Our experience with the burn cases makes us hopeful that chest cases of this type may respond favorably to full nitrogen replacement.

Consequence of Large Protein Loss. Some of the consequences of large protein loss have been implied in the remarks on wound healing and on the maintenance of tissue integrity and need not be repeated. When the loss is large and acute, such as that which occurs in burns, the osmotic component of the blood can be so depleted as to cause shock.

TABLE IV
NITROGEN VALUES OF VARIOUS HOSPITAL DIETS

	<i>Protein gm</i>	<i>Total N gm</i>	<i>N in gm kgm</i>
Basic	70	11.2	186
High Protein (1)	120	19.2	32
High Protein (2)	130	20.8	346
Tolerance ¹	192	30.7	512

¹ By tolerance is meant the amount taken to the point of satiety

In the cases of more chronic losses, although the hypovolemia may be better tolerated, the patient must be expected to be a poorer risk as a result of the hypovolemia.

The blood plasma level does not always indicate a diminished total blood protein but it may be safely stated that a blood plasma protein below 6.0 grams per cent is indicative of protein deficiency. Five grams per cent is usually called the critical level of clinical edema.¹⁰

Digestive disturbances in the form of delayed emptying time and even of vomiting and diarrhea⁶ may be symptoms. This would cause a vicious circle in further decreasing the intake.

There is also evidence to show that antibody formation is hindered.¹⁸

A set of mental symptoms in the form of confusion, apathy and incontinence of urine and feces has also been noted to be associated with protein deficiency.

Lastly, convalescence appears to be retarded by protein losses which are not replaced, resulting in long continued weakness and incapacitation. This we shall discuss later.

Inadequacy of Natural Food Assuming that the replenishment of the nitrogen lost is both desirable and feasible, the question arises as to the adequacy of natural food for this purpose. Table IV shows the range of nitrogen values of the standard hospital diets. It will be seen that the ceiling of nitrogen intake is set by the "high protein diet" which contains approximately 20.8 grams of nitrogen. Considering that it takes more than 1 gram of nitrogen in the intake to replace 1 gram of nitrogen lost from the body, it is readily understandable how inadequate this

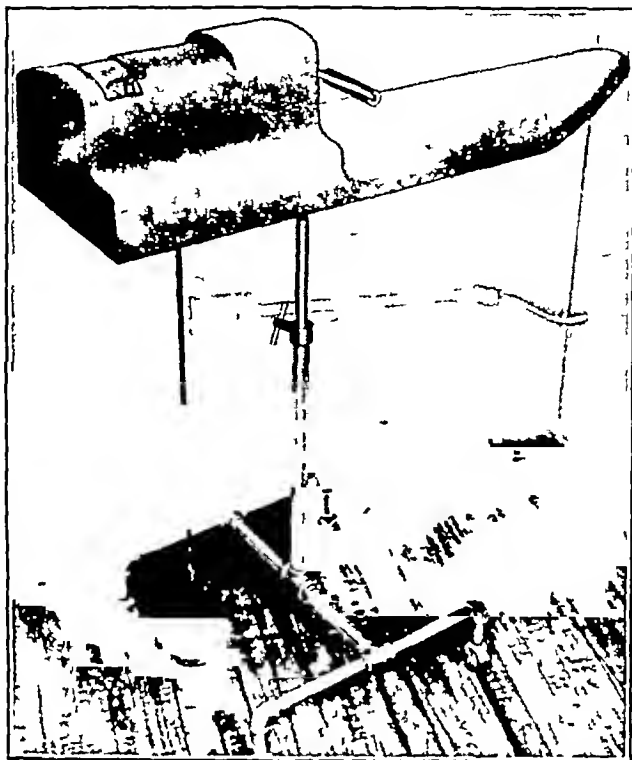


Fig 1 Improved bedside ergograph with mechanism enclosed

“high protein diet” is to a person who is losing 20 grams of nitrogen in the urine and 6 to 9 grams in an exudate. The gap between the low ceiling of nitrogen intake possible with natural food and the large losses occurring in trauma and disease can be filled to a fair degree of adequacy by protein hydrolysates such as amigen.

Convalescence I shall now take up our studies on convalescence in five clinical categories, namely, burns, gastrectomy, herniotomy, cholecystectomy, and finally peptic ulcer, and incidentally show the value of hydrolysates. Except for the cases of burns, the complete nitrogen balance was followed in all of the cases for from a week to twelve days. Also determined were the body weight and in many cases, the endurance as tested by the bedside ergograph.

The original model of this ergograph was described in a previous communication.¹⁹ The improved model is shown in Figure 1. The E T or ergograph time is the number of seconds a patient is able to lift a known weight until fatigue sets in. Objection to the use of the ergograph has been advanced on the basis that both motivation and the

TABLE V

NITROGEN INTAKE IN PATIENTS WITH BURNS FED WITH
PROTEIN HYDROLYSATES

Patient	Original Body Wgt Kgm	Area Burned %	Total Daily N Intake gm	g N in gm Wt Kgm	Equiv Plasma cc	Remarks
J C	56.8	10	35	0.62	3644	Sufficient
J McN	55.45	30	24	0.43	2500	Insufficient
			25.6	0.46	2650	Insufficient
			33.6	0.61	3500	Maintenance
			42.2	0.76	4400	Rapid Gain
M W	65.9	50	27.44	0.42	4570	Insufficient
			36	0.55	3750	Maintenance
			49.5	0.75	5160	Slight Gain
			66	1.00	6875	Rapid Gain

learning process, which have been found to affect ergography on normal subjects, may introduce sources of error in tests in convalescence. However, the factor of motivation in severely ill patients may be considered a minor one, since most patients are eager to show as good results as possible. The matter of training may also play but a small part, since these tests were made not more often than once in two or three days. In any event, the results have been striking and consistent, showing a gradual increase when the patient improved and was on positive nitrogen balance, and a decline when the patient declined and was on negative nitrogen balance.

The period of recumbency has also been taken as a criterion of recovery, although it is only a relative one, since the practice of forced early ambulation has itself shortened convalescence, perhaps by stimulating appetite and promoting an earlier establishment of positive nitrogen balance. The patients reported in these five groups were all from a surgical service that does not practice early ambulation, so that the factor of more prolonged bedrest is common to all.

Burns. I shall first take up three cases of burns as shown in Table V which have been reported elsewhere.²⁰ It will be seen from the table that there seems to be a fairly close relationship between the area of burned surface and the amount of nitrogen intake necessary to maintain nutrition. Thus, J C, who had only 10 per cent of his body area burned,

TABLE VI
LOW NITROGEN INTAKE POSIGASTRECTOMY

Name	N Intake Wt gm	N Loss Wt x Day gm	Days Under Study	Loss of Wt, Kg	Return of E T, Days	Days in Bed	Remarks
P B	04	153	8	4 27	Not 12th	23	Evisceration
F Mc	04	015	12	6 59		17	
J S	04	207	8	3 89		17	
D I	052	165	11	9		35	
N G	06	—	12	7 8		24	
A D	07	183	10	4 78	Not 12th	19	Amigen-prepared
G W	08	089	13	5 26		17	
R B	095	159	8	48		21	
F W	095	065	12	4 45		21	
M K	11	237	9	6 19		18	
W C	18	088	9	4 05		18	Amigen-prepared
J B	19	078	10	1 7		37	
A S	27	015	9	4 37		17	
Average Days						21 07	

was able to support nutrition on 35 grams of nitrogen in the form of amigen. For J McN with 30 per cent of body surface burned, 25.6 grams nitrogen was insufficient, 33.6 maintained nutrition, whereas 42.2 resulted in rapid gain. M W with 50 per cent of body surface burned, lost ground on 27.44 grams nitrogen, was maintained on 36 grams, registered slight gain at 49.5, and rapid gain at 66. All these values are much larger than the amount of nitrogen available in even the hospital high protein diet.

Gastrectomy, Cholecystectomy and Herniotomy The next series were gastrectomy cases. There are thirteen cases on low protein intake in Table VI, the intake ranging from .05 to .27 grams of nitrogen per kilogram body weight. The nitrogen losses/KBW ranged from .015 grams [19 GM/KBW] in the case of F Mc to .237 in the case of M K. The body weight loss ranged from .48 kilograms in the case of R B to 6.59 kilograms in the case of F Mc. The strength as measured by the

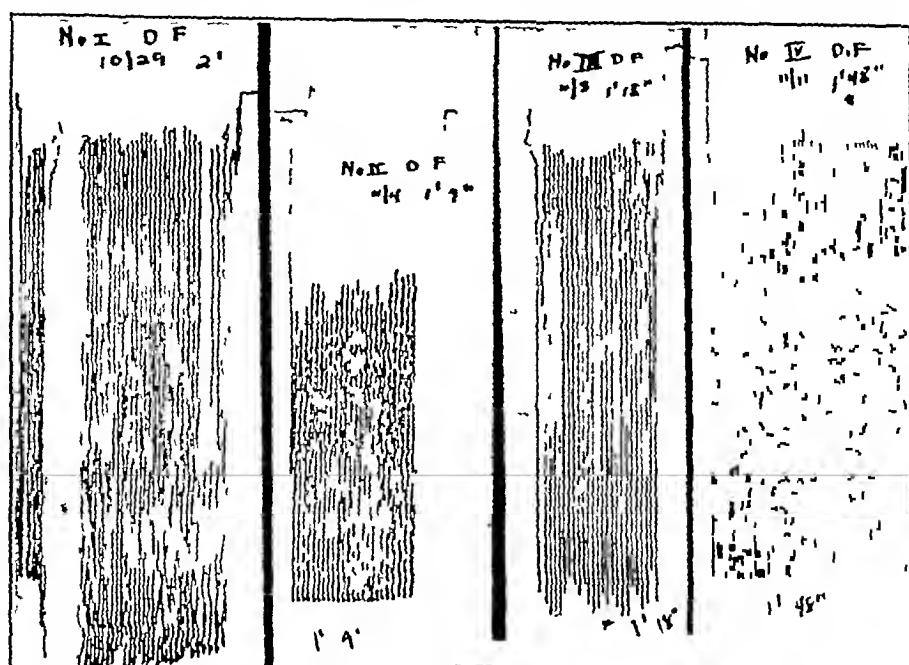


Fig 2 Ergogram of Patient DF (Table VI) Low protein intake postgastroctomy Initial ergogram E1 was 2' The three subsequent ergograms were respectively 6, 10 and 13 days after operation Note that on the thirteenth day, ET had not returned to the initial reading

TABLE VII
HIGH NITROGEN INTAKE POSTGASTRECTOMY

Name	N Intake Wt gm	N Gain Wt x Day gm	Days Under Study	Wt, Gain kgm	Return of Endurance	Days in Bed
AV	25	069	7	1 14		22
GH	42	049	13	2 2		13
VB	434	169	12	4 71		14
PR	44	077	8	4 51		8
GS	44	—	8	6 0		8
AV	48	14	11	4 54	Before 8th	9
FR	482	217	11	3 95		17
AH	5	—	—	4 0		10
CN	6	212	12	5 3	Before 8th	10
RB	6	241	10	4 32	Before 8th	10
EB	61	303	11	5 85		10
PF	692	2	12	4.21		14

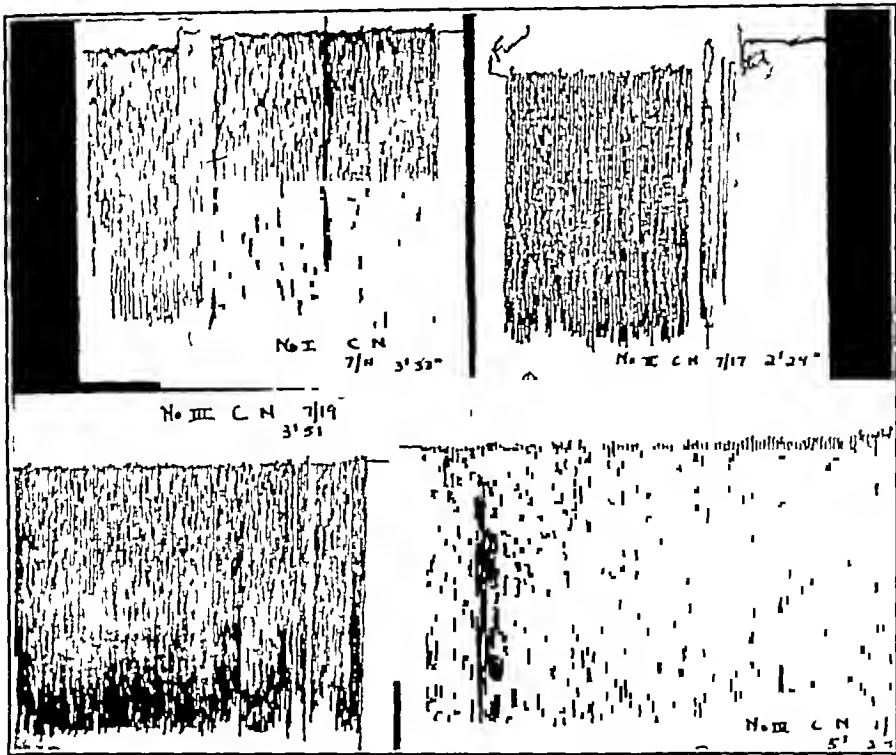


Fig 3 Ergogram of Patients CN (Table VII) High protein intake, gastrectomy case Panel I is the initial ergogram Subsequent ergograms, 4, 6 and 12 days after operation Note that by the sixth day, the E T had topped the initial reading

ergograph had not returned by the twelfth day in any of the patients tested Figure 2 shows one such an ergogram The average number of days which the patient stayed in bed was 21.07 M K and W C were both fed with amigen until they felt strong and gained weight at least a week before they were sent to the operating room Their ability to get up in thirteen days indicates the importance of the pre-operative period of up-building and the usefulness of hydrolysates in the up-building of malnourished patients

Table VII summarizes twelve similar cases on high nitrogen intake following gastrectomy, the nitrogen and caloric intake again consisting of amigen and dextri-maltose fed for the first four to six days through the jejunal lumen of a double-lumened tube, the other lumen lying in the stomach for the purpose of keeping the viscus deflated After withdrawal of the tube the feeding was given orally It will be seen that the level of intake was 25 grams of nitrogen/KBW or over All the patients

were in positive nitrogen balance, gaining from 0.69 grams of nitrogen per KBW in the case of A V to 3 in the case of E B. The weight gain ranged from 1.14 to 6 kilograms. The endurance returned by the eighth day, and Figure 3 shows the ergogram of C N. The number of bed days averaged 12.8, an average which was not quite fair since any attempt at a reduction of bed days in patients of this type runs counter to surgical tradition and is usually resisted, eventually resulting in a prolongation of bed rest. The final number of eight to nine days is therefore the more faithful time of bed rest.

Putting these two tables together, one finds that under an intake of 19 GM/KBW the patients were always in negative nitrogen balance and lost weight and that the E T declined significantly in all the cases tested. One patient, A V, with an intake of 25 grams nitrogen per KBW* was in positive balance, whereas another patient, A S, was in negative balance on 27 grams nitrogen per KBW, denoting that there is an intermediate zone in which some cases will register a negative balance while others, a positive balance. All patients having an intake of 42 grams per KBW and over were in positive nitrogen balance and all gained weight, and all those tested showed an early return of endurance as shown by the early decrease of E T. Both of these tables were rearranged from tables which appeared in two previous reports^{20, 21}

The third series of cases were cholecystectomy cases which are represented in Table VIII under both low and high intakes. In this series, when the intake was below 224 grams per KBW, there was a negative balance, whereas above 339 grams per KBW, there was always positive nitrogen balance. The weight and ergogram show the same trend as in the gastrectomy cases. This series is still too small, as there is too large a gap between the unit intakes of 224 and 339 grams per KBW.

The last series are seventeen cases of hernioplasty, twelve unilateral and five bilateral. This study was undertaken not because the nitrogen loss after herniotomy is an apparently important factor in convalescence but to test the theory that normal persons subjected to operative trauma undergo a nitrogen loss which cannot be replaced. Most of these patients were in good nutrition, so that except for their structural defects, they may be considered normal persons who had suffered operative trauma.

Table IX summarizes the nitrogen balance studies. Part A embodies the twelve cases of unilateral hernioplasty and Part B, the five of bi-

* In the balance of this paper "KBW" will denote Kilogram Body Weight

TABLE VIII
NITROGEN INTAKE POST-CHOLECYSTECTOMY

Name	N Intake Wt, gm	N Gain or Loss Wt x Day	Days Under Study	Wt, Gain or Loss (kgm)	Return E T (day)	Bed Days
A C	089	— 104	12	— 39	not on 14th	35
A J	058	— 12	10	— 28		18
M R	224	— 026	14	— 136		19
R V	339	168	10	274		10
P F	348	143	10	277		12
E S	382	082	12	12	6th	12
L M	402	3285	10	37		8
A S	43	049	10	117	8th	10
F S	456	204	12	10		12

TABLE IX
UNILATERAL HERNIOPLASTY Group A

Name	N Intake gm per kgm	N Balance per day	Number of Days	Wt Change (kgm)	E T
A S (1)	059	— 111	9	— 102	
(2)	087	— 086	9	— 159	
A B	104	— 06	10	— 137	273-243
O V	131	— 07	10	— 15	377-260
V P	147	— 011	10	— 45	500-510
J B	182	011	10	— 37	
H G	258	002	10	5	
P N	35	046	10	0	372-390
W J	363	045	7	?	
M S	38	11	10	201	
J F	45	131	10	202	
D F (1)	446	127	10	222	
(2)	454	147	8		
J D	53	033	10	159	

BILATERAL HERNIOPLASTY Group B

A T	13	— 152	10	— 29	
S J	156	— 072	10	— 227	
B A	335	066	8	9	
C L	373	003	10	3	
J F	395	004	10	31	

lateral A S and D F in Part A both had bilateral hernias, one of which was operated upon several days after the other. It will be seen that at the second operation the loss of nitrogen in grams per KBW did not differ radically from the first operation a week or so earlier. It will also be seen that on an intake of 182 grams per KBW, there was a negative nitrogen balance. The ergograph time (E T) in this group with the negative nitrogen balance was significantly depressed in one, O V, and very slightly but not significantly in two, that above 258 grams per KBW there was a consistent positive nitrogen balance with gain in weight.

A comparison of the nitrogen loss or gain per KBW in simultaneous, bilateral hernioplasty with that in unilateral hernioplasty is interesting. Thus, if we match A T in Group B, intake 13 grams per KBW, with O V in Group A, intake 131 grams per KBW, we see that A T lost 152 grams nitrogen per KBW, as compared with the loss of only 07 grams in O V, and the weight loss of the former was 2.9 kilograms as compared with 1.5 in the latter. S J in Group B, with an intake of 156 grams per KBW, if matched with V P in Group A, who had an intake of 147 grams per KBW, lost 072 grams nitrogen per KBW, while V P lost only 011 grams. The weight loss of S J was 2.27 Kgm as compared with the loss of only 45 Kgm in V P. Again, if C L, with unit intake of 373 grams of nitrogen is matched with W J with unit intake of 363, it is seen that C L gained only 003 grams of nitrogen per KBW, whereas W J gained 045. Lastly, if J F, Group B, with intake of 395 grams per KBW is matched with M S on 38 grams per KBW, it will be seen that the former gained only 004 grams per KBW, whereas the latter gained 11 grams.

These figures suggest that the loss of nitrogen in hernioplasty may not all be attributable to the nitrogen loss due to bedrest and that the extent of operative trauma plays a role. It also shows that the post-operative loss of nitrogen, even in previously normal persons, is correctable, at least in some types of cases. Both Elman²² and Peters²³ have also found that cases of hernioplasty can be readily put into positive nitrogen equilibrium.

Parenthetically, the hope may be expressed that herniotomy cases in good nutrition, because of the fairly well standardized surgical trauma inflicted, may be used to compare the biological value of different hydrolysates on the human body. Thus, if a hydrolysate X cannot support

N equilibrium at a level of intake of about 182 grams nitrogen per kilogram body weight, it would be inferior to amigen, while one which can do this at a lower level might be considered of superior biological value

A correlated view of the studies of these four surgical categories, namely, burns, gastrectomy, cholecystectomy and herniotomy, suggests that there may well be a critical level of nitrogen intake peculiar to each category to maintain the patients in nitrogen equilibrium. Only a further study will confirm or refute this possibility.

Peptic Ulcers The fifth series of cases is of peptic ulcers treated with protein hydrolysates and high caloric diet. The series of twenty-nine cases may be classified as follows:

16	duodenal ulcer
5	duodenal and gastric ulcer
6	gastric ulcer
2	gastro-jejunal ulcer
<hr/>	
29	
18	"intractable"
6	with retention (20-100%)
6	with frank hemorrhage

All were treated with from 5 to 6 grams nitrogen per KBW, in the form of amigen, and enough dextri-maltose to make up to 40 C per KBW. This is approximately 5 grams each of amigen and dextri-maltose per KBW. The mixture is suspended in water, divided into eight to nine feedings, and given at two-hourly intervals. Feedings were continued two or three weeks exclusively, depending upon the clinical response and x-ray findings. No antacids or antispasmodics were given, and wherever necessary, amphojel in 4 cc doses was given twice a day to control diarrhea. A full complement was added to the feeding. The results may be summarized as follows:

Pain and distress stopped in twenty-four to forty-eight hours. Vomiting stopped forty-eight hours after institution of the feedings, rapid roentgenologic healing, positive nitrogen balance, averaging 10 to 16 grams (first ten days), gain in weight, 1 to 8 Kilos in two to three weeks, and rapid gain in strength and morale. However, the treatment does not prevent recurrence on resumption of old dietary habits.

Figures 4 and 5 show the progression of healing in two gastric ulcer cases. One interesting feature in connection with these ulcer cases is the great improvement in endurance as may be seen in the ergogram of patient E B in Figure 6.

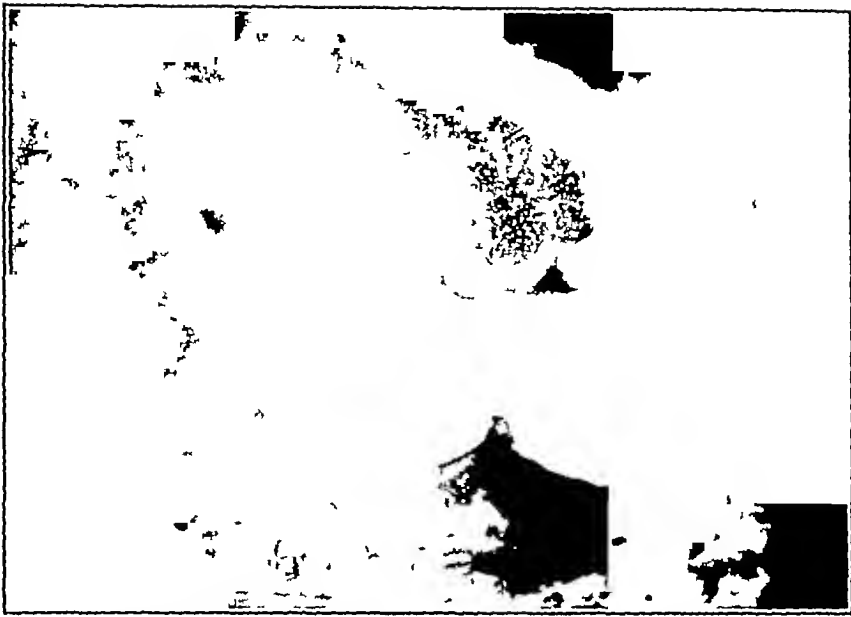


Figure 4A Patient C.B. Large crater, lesser curvature



Fig 4B Patient C.B. Almost complete healing in 10 days



Fig 5A Patient R B Large ulcer crater, lesser curvature pars media



Fig 5B Patient R B Shows gradual filling up of defect 10 days after treatment



Fig 5C Patient R B Four weeks after treatment. Note nipple-like defect.



Fig 5D Patient R B Six weeks after treatment. Note stalk-like defect.



Fig 5E Patient R B Seven and a half weeks after treatment. Note almost complete healing

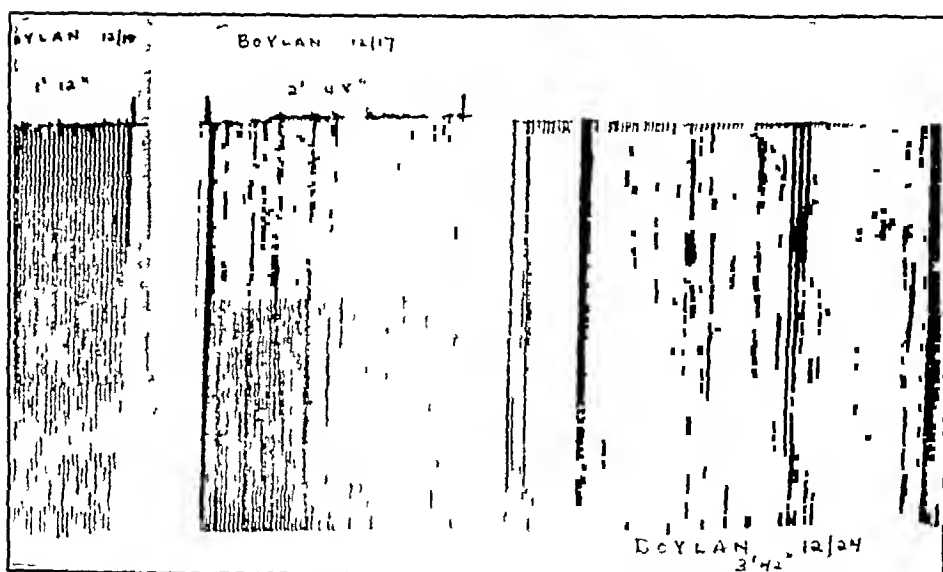


Fig 6 Ergogram of ulcer patient CB Panel (a) initial ergogram, ET 1'2", Panel (b) ET 2'48", 6 days after treatment, Panel (c) ET 3'42", 2 weeks after treatment.

TABLE X

EFFECT OF FEEDING MIXTURE ON pH AND FREE ACIDS IN THE GASTRIC JUICE OF A PEPTIC ULCER PATIENT

<i>Time</i>	<i>pH</i>	<i>FA</i>	<i>TA</i>
10 00	2 05	47 0	65 5
10 10	1 92	59 0	78 5
Feeding 10 10			
10 45	4 21	—	205 5
11 00	4 24	—	269 5
11 15	4 15	—	245 5
11 30	4 07	—	305 0
11 45	4.22	—	298 0
12 00	4 18	—	286 5
12 15	3 68	3 0	212 5
12 30	3 01	34 5	191 5
Amigen 51 1 g Dextrin-maltose 58 6 g			
Formula	5.22	—	456 0

Another feature of this treatment is that where obstructions were found in the six-hour x-ray plates, they were relieved in twenty-four hours by amigen feeding. The significance of this point will be commented on later.

The question arises: What is there in protein hydrolysate feeding which may account for these prompt results? Amigen is an amphoteric substance and the addition of it to a hyperacidic gastric juice raises the pH to almost the point of abolition of peptic activity. Table X shows that the pH of a gastric juice, originally between 1 92 and 2 05, was raised by the feeding of a mixture of 51 1 grams of amigen and 56 8 grams of dextrin-maltose to 4 24. The free acid originally was reduced to zero for about an hour and fifteen minutes. After that, the pH began to decline and the free acid to rise. It is perhaps this action of neutralization of the acid in connection with the giving of a rich nutrient solution to enable the body to build up its tissue deficiency which accounts for the prompt healing in these cases. Thus it seems that by the peculiar virtue of its being both an antacid and a rich nutriment,

TABLE XI

PATIENT WITH GASTRO-JEJUNOCOLIC FISTULA FED WITH PROTEIN HYDROLYSATES

<i>A S</i> <i>Date</i> <i>1942</i> <i>Feb 29</i> <i>to</i> <i>March 1</i>	<i>N Intake</i>	<i>Nitrogen Output</i>			<i>N Bal</i> <i>gms</i>	<i>P.P</i> <i>gms %</i> <i>A/G</i>	<i>Wt</i> <i>Kgms</i>	<i>Remarks</i>
		<i>Urine N</i> <i>gms</i>	<i>Fecal N</i> <i>gms</i>	<i>Total N</i> <i>Output</i> <i>gms</i>				
March 1	11	10.28	3.36	13.64	-2.64	5.25	47.9	Lost 15 lb
1-2	8	9.42	4.41	13.83	-5.83			8 weeks x-ray
2-3	9.4	8.74	4.85	13.59	-4.19	5.15	47.3	G-J-C- fistula
3-4	14.58	10.61	1.04	11.65	2.93			"Stronger"
4-5	14.58	11.38	1.03	12.69	1.89		47.8	
5-6	8.46	7.24	1.58	8.82	-0.36			
6-7	8.8	7.94	1.14	9.08	-0.28		47.3	"Weaker"
7-8	18.9	16.85	1.06	17.91	.91	5.25		
8-9	18.9	13.27	1.21	14.48	4.42			
9-10	18.9	14.08	1.47	15.65	3.25			
10-11	18.9	15.18	1.37	16.55	2.35			
11-12	18.9	15.06	1.45	16.51	2.39			
12-13	18.9	14.87	1.26	16.13	2.77			
13-14	18.9	16.48	1.48	17.96	0.94	6.1	49.1	x-ray healed "strong"

amigen and perhaps other hydrolysates are specially suitable for the treatment of peptic ulcer

Value of Hydrolysates The studies in the cases of burns, gastrectomy, cholecystectomy and herniotomy show how valuable hydrolysates are in conditions in which natural food cannot be ingested or ingested only in quantities insufficient to replace increased nitrogen loss due to disease. Whereas the nitrogen intake in the natural diet is generally limited to the 20.8 grams (34% grams/KBW for a 60-Kgm man) in the high protein diet, the intake possible with protein hydrolysates may be many times that amount. By the intravenous route, 3 liters of a 5 per cent amigen may be safely given. This is equivalent to 3 grams/KBW. By mouth, it has been found that most patients can tolerate as much as 8 grams of nitrogen per Kgm without having diarrhea.

If both routes are simultaneously utilized, a total of 11 grams of nitrogen per KBW may be given, over 500 per cent of the intake possible with natural food. It is quite possible that further research in this field will make available a product which can be given in greater concentration and which will be of maximum human biological value, thus further raising the ceiling of replenishment.

However, hydrolysates have another field of usefulness. The cases of pyloric obstruction following peptic ulcer which were relieved twenty-four hours after amigen feeding, suggest that hydrolysates are better tolerated by a diseased gastro-intestinal tract than natural food. Additional evidence for this may be seen in Table XI which summarizes the nitrogen balance study of A.S., a 48-year old man who was admitted with a gastro-jejuno-colic fistula, having lost 15 pounds in three weeks. During the first three days on the natural diet, the patient was losing in the stool from 3.36 to 4.85 grams of nitrogen per day or almost half of his intake. This was accompanied by negative nitrogen balance, weakness and loss of weight. He was then put on amigen by mouth, taking an amount corresponding to 14.58 grams of nitrogen daily. This was followed by a reduction of fecal loss of nitrogen to over 1 gram and a sense of returning strength and well-being. The intake was again reduced to 8.46 for two days, at which time he was again in negative balance and feeling weaker. After that, on an intake of 18.9 grams of nitrogen, he was on positive nitrogen balance which continued for about a week, at which time the x-rays showed the fistula to be apparently healed.

We may also mention three cases of ulcerative colitis treated with amigen, in whom the nutrition was maintained although the pathological condition was not improved.

A case of pernicious vomiting of pregnancy may also be reported. A tube was passed into the stomach through one nostril and amigen feeding was instituted, at which time the vomiting stopped. This feeding was continued for three days until the nasal irritation caused by the tube became so marked that the tube had to be withdrawn. The tube was replaced in another twenty-four hours through the other nostril and a feeding period of three days was instituted. Thus a "lean" period of one day alternated with a "fat" period of three days until after four weeks the patient was able to tolerate food. The patient went to term uneventfully. This better tolerance on the part of a pathologic gastro-

intestinal tract for hydrolysates may be expected, since it is spared the task of having to take food apart and since the minimum of digestive effort is called for before absorption takes place

One is led to speculate how worthwhile it would be to try feeding this substance in other conditions in which the gastro-intestinal tract cannot tolerate natural food, such as sprue, typhoid fever, etc

In the use of hydrolysates one has to make sure that in the intravenous form they are not toxic, not anaphylactogenic, non-pyrogenic, and non-irritating to the site of injection. In the oral form, efforts are still being made by manufacturers to produce a good-tasting preparation and one which can be given in large amounts without causing diarrhea or vomiting. For both oral and intravenous preparations we must insist that they maintain positive nitrogen balance in the human being. Finally, the clinician who uses them must think quantitatively not only in terms of nitrogen but in terms of adequate caloric intake. Otherwise, the results will not be satisfactory.

Assay of Protein Nutritional Status In conclusion, some general comments on the assay of the nutritional course of a convalescent patient may be pertinent. At present there are four likely methods of doing this: 1) nitrogen balance, 2) plasma protein curve, 3) body weight curve, and 4) the bedside ergograph.

Nitrogen balance determinations require a tedious and rather complicated chemical procedure not available to the average hospital. It depends for its validity on a bookkeeping process which as evidence is at best only circumstantial and not directly concerned with the effects on the body occasioned by the nutritional state.

The other three methods are more closely connected with assay of the body status. However, none of these methods is sensitive. A large amount of plasma protein could be lost from the blood without its being reflected in the plasma protein level, and hydration and dehydration can cause marked swings in the values. The body weight is also subject to the factors of hydration, to retention of urine and feces. It is inconvenient and not easily measured in the bed patient without adequate personnel.

As mentioned before, the ergograph has the theoretical objections of motivation and the learning factor. However, it has seemed to us that the changes in endurance produced by nitrogen loss are so striking that the ergograph findings transcend these two factors. The ergograph de-

terminations are sensitive enough to be of clinical usefulness, and in conjunction with the other three methods, the ergograph is a valuable tool. Serial readings of all three are more valuable than single determinations.

SUMMARY

1 Proteins are essential to wound healing, to the maintenance of tissue integrity, and from present indications, to expeditious convalescence. Protein deficiency endangers all three.

2 A patient can become protein-deficient as a result of inadequate intake and increased nitrogen output or a combination of these two factors.

3 Decreased intake may be due to the patient or neglect on the part of the attending staff.

4 Increased output may be due to increased metabolic loss and to the loss through exudates.

5 The ceiling of nitrogen intake in natural food is naturally low and consequently natural food is often inadequate to replenish the increased protein loss in disease and injury.

6 Studies on cases of burns, of postoperative gastrectomy, cholecystectomy and herniotomy, suggest that convalescence can be shortened, strength and weight conserved by full caloric and nitrogen replacement immediately postoperatively, and that there may be a critical range of nitrogen intake for each disease category.

7 The protein hydrolysates, by raising the ceiling level of nitrogen-intake, are indispensable in many disease conditions and can be used with greater elasticity than natural food.

8 In the course of study on the value of protein hydrolysates, a new treatment for peptic ulcers has been evolved.

9 Protein hydrolysates for clinical use must fulfill a number of criteria and clinicians using them must be quantitatively-minded.

10 A discussion on the assay of the nutritional course of convalescent patients has been attempted.

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FACTORS DETERMINING THE DOSAGE OF PENICILLIN IN THE TREATMENT OF INFECTIONS*

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IT is now well established that penicillin is an extremely effective agent for the treatment of many different types of infections, but a review of the clinical reports makes it at once evident that there is little agreement concerning the amount, or the mode or frequency of administration required to effect a satisfactory therapeutic response. Due to the scarcity of the drug there was at first a tendency to administer small amounts, and as a result erroneous impressions arose concerning the effectiveness of penicillin in diseases such as subacute bacterial endocarditis. More recently, doses found arbitrarily to give satisfactory results have been recommended by various groups of investigators. An example of the discrepancies resulting from this procedure is the recommendation, in cases of staphylococcal sepsis treated with a continuous intravenous infusion of penicillin, of 30,000 to 40,000 units daily by one group,¹ while in the opinion of others 300,000 to 400,000 units should be administered each day.²

Now that penicillin is readily available, it is desirable to review the laboratory and clinical experiences which have helped to clarify many of the confusing problems of dosage and mode of administration. The purpose of the present report, therefore, is to bring together the important contributions which provide a basis for rational therapy.

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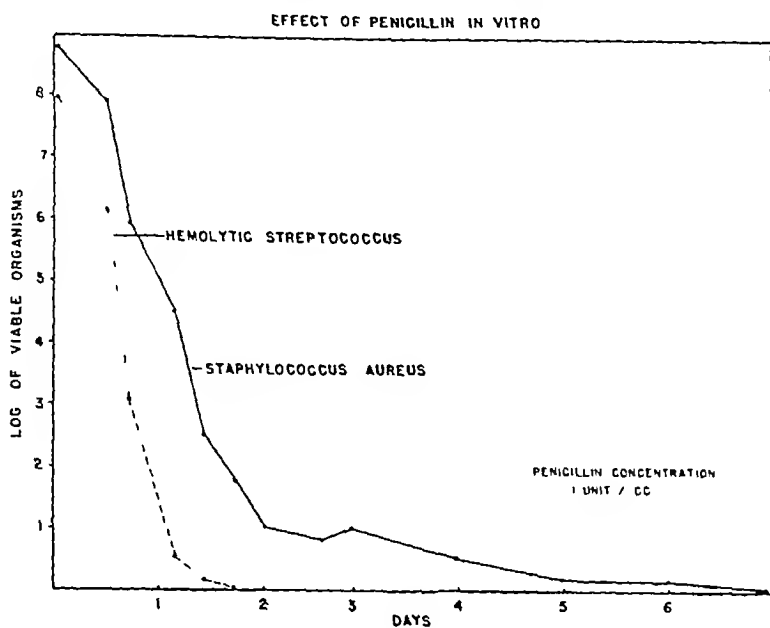
Two outstanding characteristics of penicillin are its high degree of antibacterial action and its selectivity. In contrast to the sulfonamides whose action is primarily bacteriostatic, penicillin in concentrations obtained in patients causes sterilization of cultures of susceptible organisms within 24 hours and is for this reason often referred to as a bactericidal agent. Unlike true bactericidal substances such as the phenols, which sterilize cultures within a few minutes, penicillin even in high concentrations does not cause death of microorganisms unless the contact is maintained for many hours.³ Of great practical importance, however, is the fact that both *in vitro* and *in vivo* penicillin is much more effective in its antibacterial action than the sulfonamide drugs.

Selectivity refers to the high degree of antibacterial activity obtained by penicillin against gram-positive bacteria, and its failure to inhibit the growth of the majority of gram-negative bacteria.

Variations in susceptibility to penicillin occur not only among different species of bacteria, but also among various strains of any one species. With most penicillin sensitive bacteria, however, and particularly with the pneumococcus,⁴ beta-hemolytic streptococcus,⁵ and gonococcus,⁶ these variations are not of clinical significance since they are not of sufficient magnitude to affect the results of therapy. For this reason, routine sensitivity tests of the infecting organisms are of no practical value to the clinician in most diseases for which penicillin is employed. There are exceptions, however, for example in certain staphylococcal infections, and in patients with subacute bacterial endocarditis in which the etiological organisms may be penicillin resistant streptococci (enterococci), knowledge of the sensitivity of the organism may be of importance both from the standpoint of therapy and prognosis.

Correlation between the *in vitro* sensitivity of various organisms and clinical results obtained in patients is much closer with penicillin than with the sulfonamides. This is probably due to the fact that substances such as pus and exudate which inhibit the sulfonamides, do not impair the action of penicillin.⁷ Indeed, under certain conditions, by promoting the multiplication of bacteria these substances actually seem to enhance the antibacterial action of penicillin.⁸

In view of the frequency with which various organisms acquire resistance to the sulfonamides, the problem of penicillin resistance has received intensive study. Laboratory investigations indicate that re-



sistance of the beta-hemolytic streptococcus,^{9 10} gonococcus,¹¹ pneumococcus,¹⁰ and most other susceptible organisms develops only after prolonged exposure to penicillin. Clinical experience has confirmed these observations, with the exception of the staphylococcus, well substantiated instances of penicillin resistance acquired during therapy have not been described. Further, in patients with streptococcal, pneumococcal, and even staphylococcal infections, in whom relapses occurred because of the location of the organisms in relatively avascular areas, penicillin therapy has been continued for many weeks without the development of any measurable degree of penicillin resistance.^{12 13} Final conclusions cannot be drawn, but the evidence so far available suggests that, with the exception of infections caused by the staphylococcus, penicillin resistance will not become an important clinical problem.

The behavior of the staphylococcus when exposed to penicillin differs from that of other organisms. In contrast to the beta-hemolytic streptococcus, for example, whose growth is completely inhibited by penicillin in 24 to 36 hours, viable staphylococci can often be recovered from cultures for as long as 6 or 7 days (see Figure 1). Clinically, the same situation is observed in patients with empyema. In streptococcal and pneumococcal empyemas the administration of intrapleural penicillin for 1 or 2 days causes complete sterilization of the fluid, while in

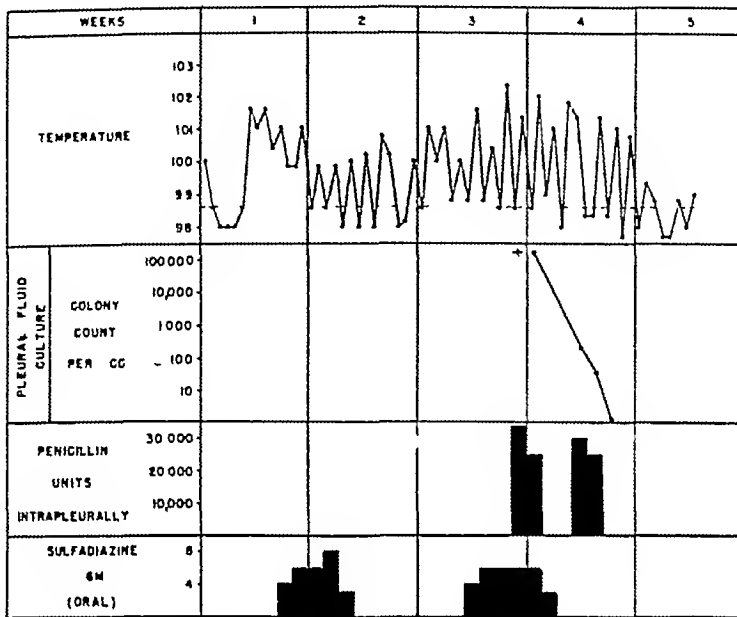


FIG 2—Antibacterial effect of penicillin in staphylococcal empyema

staphylococcal infections of the pleural cavity treatment must often be continued for at least a week. An illustrative case of staphylococcal empyema is presented in Figure 2. Twenty-four hours after the initial intrapleural injection of 40,000 units of penicillin the fluid contained 100,000 organisms per cc, on the 4th day there were 100 organisms per cc, and sterilization was not effected until the 7th day.

Staphylococci which remain viable for several days in the presence of bacteriostatic concentrations of penicillin are often penicillin-resistant, and contain an enzyme-like substance, "penicillinase", which in small quantities destroys large amounts of penicillin.¹⁴ The relationship of this substance to other "penicillinases" has not been elucidated, but it is probable that studies of various penicillin inactivators will reveal valuable information concerning the basic structure and mode of action of penicillin. Penicillin resistance has been observed in approximately 10 per cent of strains of staphylococci isolated from clinical sources.^{9, 15} Whether resistance occurs as an acquired characteristic as a result of contact of the bacteria with penicillin, or whether the sensitive organisms are eliminated leaving naturally resistant staphylococci is not definitely known, but recent studies of two independent investigators^{16, 17} support the latter possibility. The evidence further suggests that re-

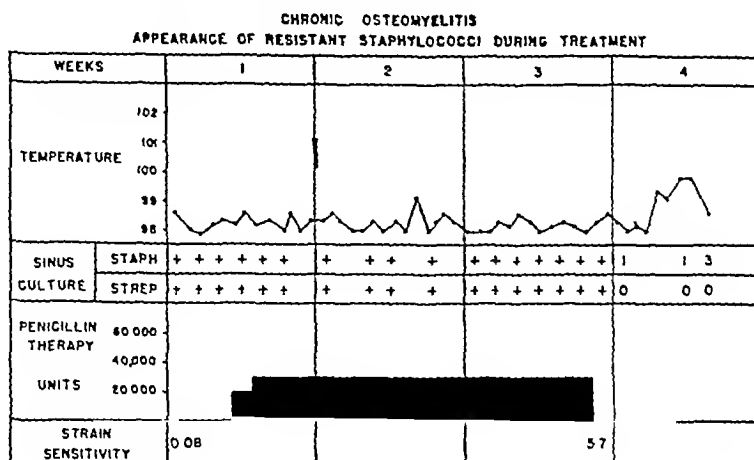


FIG 8

sistance is much less likely to be manifested if the organisms are, from the start, kept in contact with high concentrations of penicillin. The appearance of penicillin resistance in a case of staphylococcal osteomyelitis treated with inadequate doses of penicillin is presented in Figure 3. The staphylococci isolated prior to the institution of therapy were killed by relatively low concentrations of penicillin, whereas strains isolated after two weeks of treatment with penicillin in a dose of 5,000 units every 4 hours were markedly resistant. More favorable results have been obtained in other cases receiving large doses of penicillin. Here, of course, as in staphylococcal infections in general, the necessity of prolonged therapy as well as adequate doses should be emphasized.

ABSORPTION AND EXCRETION OF PENICILLIN AND ITS DIFFUSION INTO VARIOUS BODY FLUIDS

Before considering the relationship of the concentration of penicillin in the blood to antibacterial action, it is well to review briefly studies on the absorption, excretion and diffusion of penicillin. Penicillin is most frequently administered intramuscularly, although other routes may be used. When injected into the muscle, absorption is rapid, producing maximal concentrations in the blood within 15 to 20 minutes. Beginning penicillin therapy with an initial intravenous injection is therefore completely unnecessary, although it is a common procedure, presumably as a holdover from sulfonamide medication, in which an initial intravenous injection is often advisable.

Once absorbed, penicillin is eliminated from the body very rapidly.

It was originally thought that approximately 40 per cent of the dose injected was destroyed in the body,^{7, 18} but recent evidence indicates that destruction by the tissues is actually slight, and that almost all of a single dose administered intramuscularly or intravenously is excreted in the urine.¹⁰ Eighty per cent appears in the urine within two hours, and after the fourth hour the amount remaining in the body is less than 5 per cent of the original dose. By various methods of studying renal clearance it has been definitely demonstrated that the reason for the rapid elimination of penicillin from the body is that it is excreted both by the glomeruli and the renal tubules.^{20, 21}

These two factors, rapid absorption and rapid excretion, are responsible for one of the greatest disadvantages of present day penicillin therapy, namely, the necessity for frequent, parenteral injections. Intensive efforts are being made to perfect methods of delaying the absorption of penicillin, by mixing it with beeswax and peanut oil,²² by the use of vasoconstrictors,²³ and by the application of cold compresses near the site of injection.²⁴ Attempts are also being made to delay excretion by combining penicillin with substances of high molecular weight,²⁵ and by the concomitant administration of other agents, such as para-aminohippuric acid, which compete with penicillin for excretion by the renal tubules.²⁶ The most promising of these methods at present is the intramuscular injection of penicillin-beeswax mixtures, blood levels are maintained for as long as 24 to 28 hours following the administration of 300,000 units of penicillin in 1 cc. of 5 per cent beeswax and peanut oil.

Methods of administering penicillin by mouth are also being studied. The best evidence at present indicates that none of the enteric coatings, oils, or antacids, so far employed give results better than those obtained with the ingestion of penicillin dissolved in tap water. With this method, five or six times as much penicillin must be administered to produce levels equivalent to those following parenteral injections.²⁷ The increased commercial production of penicillin, plus the fact that oral preparations do not need to be as highly purified as those used parenterally, may eventually make oral administration feasible even if methods of avoiding the destructive action of the gastric juices or increasing absorption from the intestine are not evolved.

Knowledge concerning the distribution of penicillin in the body is essential for good therapeutics. In general, diffusion of penicillin into various body fluids and cavities occurs irregularly, and to a small extent

For this reason local therapy as well as parenteral injections have been used in the treatment of infections of pleural, pericardial and joint cavities. Frequently when the infection is well localized, as in empyemas, systemic administration of penicillin is not required, favorable results being obtained by local injections alone²⁸

With the usual therapeutic doses penicillin does not appear in measurable quantities in the spinal fluid of normal individuals, and as a result intrathecal administration is commonly used in patients with infections of the meninges²⁹. More recently it has been shown that with very large doses of penicillin small amounts can sometimes be detected in the spinal fluid of normal subjects³⁰ and in patients with meningitis³¹. Others, however, have found that in patients with meningitis, penicillin appears in the spinal fluid very irregularly and in low concentrations³². Although a few patients with meningitis have been cured by parenteral administration alone,³³ clinical experience has shown that others have failed to respond to such therapy³² and that in some cases bacterial meningitis has actually appeared during the course of parenteral treatment of extra-meningeal infections³⁴.

The subject is controversial, but the best evidence indicates that, for adequate and conservative therapy of staphylococcal, streptococcal and pneumococcal meningitis, both parenteral and intrathecal routes should be used. Since some strains of meningococci are relatively resistant to penicillin³⁵ and the results obtained with the sulfonamides are so favorable, the latter drugs should be used in the treatment of meningococcal meningitis. The one exception to the use of both intrathecal and parenteral injections of penicillin is syphilitic meningitis, in which results with intramuscular injections alone appear to be excellent³⁶.

There are certain conditions, notably subacute bacterial endocarditis, various forms of late syphilis, and chronic osteomyelitis, in which another important factor must be considered, namely, penetration. Early results of penicillin therapy in subacute bacterial endocarditis, using only 5000 units every four hours, were so disappointing that for a time penicillin was abandoned for the treatment of this disease. More recently, large amounts have been administered for two to eight weeks, and a fairly large number of cases have now been reported in which the infection has been eradicated. These favorable results are presumably due to the fact that with the maintenance of high, continuous blood levels of penicillin, there is penetration into the vegetations and destruction of

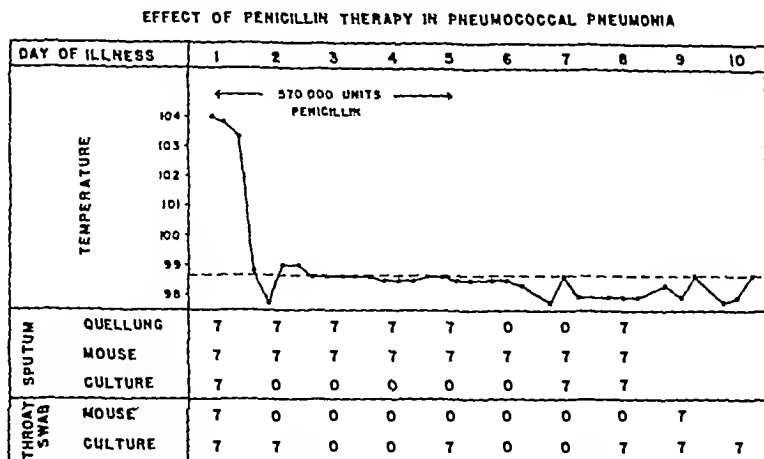


FIG 5

bacteriologically The failure to obtain a favorable response by local applications in this instance was undoubtedly due to the fact that the contact between the organism and penicillin was very brief, and emphasizes the point that relatively prolonged contact is necessary When penicillin was administered by intramuscular injection, however, the streptococci rapidly disappeared, only to reappear when treatment was discontinued after three days It has been definitely demonstrated that in order to bring about a permanent cure in cases of streptococcal sore throat, it is necessary to continue treatment for a period of at least five days³⁸

In pneumococcal pneumonia, studies by the Commission on Acute Respiratory Diseases have shown that viable, virulent pneumococci can be recovered from the sputum during and following therapy with penicillin for as long as sputum can be obtained³⁷ A representative case, showing the method of study, is presented in Figure 5 Thus, although penicillin may destroy some of the organisms present in the parenchyma of the lung, a reactivation of the infection may be caused by pneumococci remaining viable in the bronchial exudate if treatment is discontinued too soon Clinical relapses occurring in patients treated with penicillin for only two or three days have been described by Tillett, Cambier, and McCormack²⁸

With both streptococcal pharyngitis and pneumococcal pneumonia, then, it is necessary to continue treatment for several days to insure sterilization of the infected tissues and prevent relapses It would appear that penicillin merely inhibits growth of the bacteria, thereby localizing

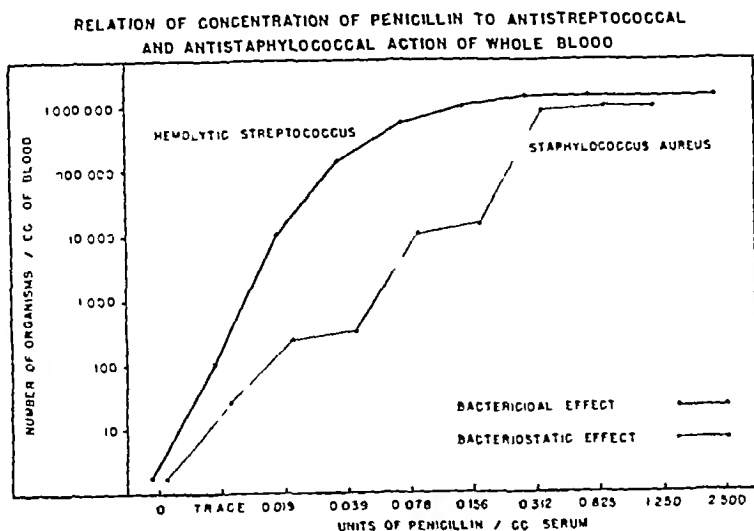


FIG 6

the infection, actual recovery is brought about by the body's own defense mechanisms. The development of natural immunity is probably of importance also in conditions other than pneumonia and pharyngitis, but so far these relationships have not been worked out in detail.

RELATION OF BLOOD CONCENTRATION TO ANTIBACTERIAL ACTIVITY

Ideally, the objective of therapy with penicillin, as with other chemotherapeutic agents, should be to maintain, at the site of the infection, concentrations of penicillin which exert maximal antibacterial activity throughout the entire period of treatment. From a practical standpoint this is not feasible at the present time, and is even considered disadvantageous by some observers,³⁰ on the basis that since penicillin is effective against bacteria only during the stage of multiplication, intermittent therapy will allow periods of multiplication alternating with periods of bacteriostasis, and will therefore be more effective. This objection to continuous therapy, based on *in vitro* observations, does not take into consideration conditions existing locally in the tissues, and from a practical standpoint the results obtained clinically with continuous effective concentrations of penicillin in the blood stream are excellent. Indications are that in the future penicillin will be administered by methods which will provide constant measurable blood levels.

In vitro tests of whole blood obtained from normal individuals receiving penicillin have shown⁴⁰ maximal antibacterial activity against

ANTIBACTERIAL EFFECT OF WHOLE BLOOD AFTER INTRAMUSCULAR PENICILLIN

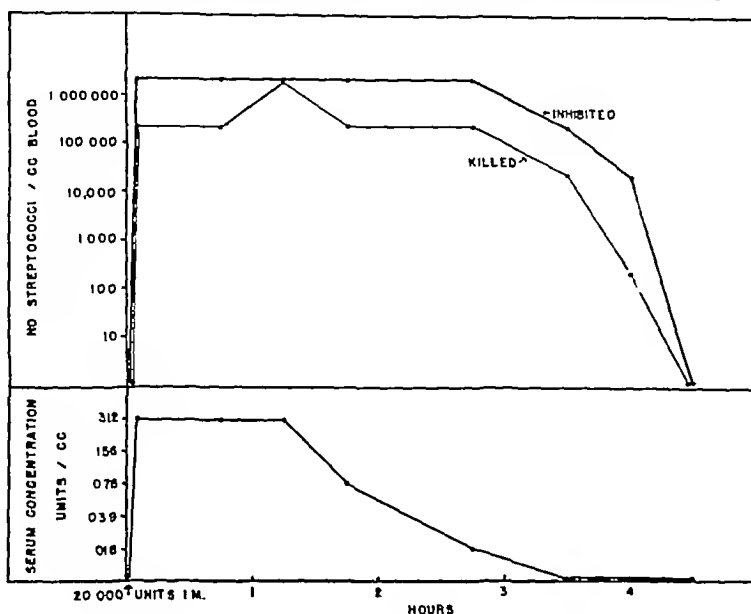


FIG 7

hemolytic streptococci and staphylococci by concentrations as low as 0.04 and 0.2 units per cubic centimeter respectively (Figure 6). Lower concentrations exhibit definite, but not maximal activity, higher concentrations do not produce any appreciable increase in antibacterial action. These values, 0.04 and 0.2 units per cubic centimeter, which apply respectively to a highly sensitive and relatively resistant organism, are of fundamental importance in relation to the concentrations obtained in the blood stream of patients.

Since chemical methods are not available, penicillin assay methods in use at the present time are based on the ability of penicillin to inhibit the growth of sensitive microorganisms. One of the defects of these methods is their inability to detect small concentrations of penicillin in body fluids. The smallest concentrations which can be measured accurately, 0.02 to 0.04 units per cubic centimeter, are highly effective against most penicillin sensitive bacteria, and it is important, therefore, to have some knowledge of how long penicillin exerts therapeutic action in the body after it can no longer be detected in the blood stream.

Bactericidal tests of whole blood obtained from patients during and following therapy have revealed valuable information on this subject.⁴⁰ In patients receiving intramuscular injections of 20,000 units, the bac-

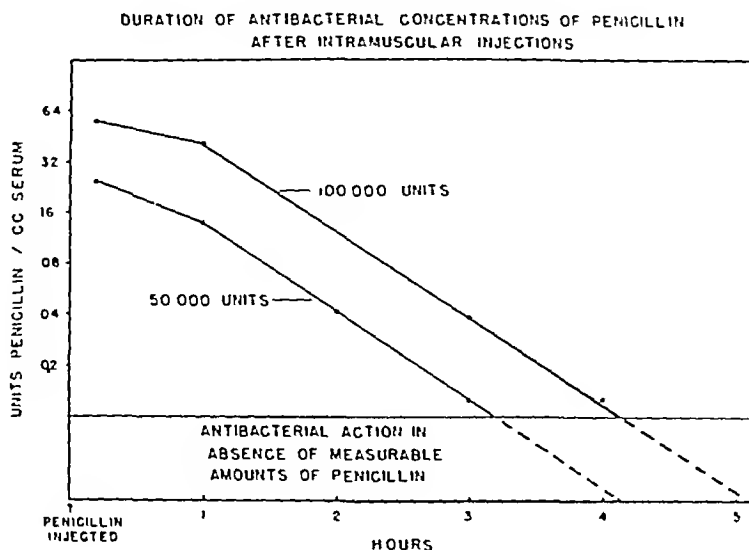


FIG 8

tericidal power of the blood was found to be increased for a period of from 30 to 75 minutes after penicillin was no longer detectable in the serum by routine assay methods. This is illustrated in Figure 7. From this evidence, it would seem highly unlikely that, following the usual injection of 15,000 to 20,000 units, one could count on any therapeutic activity for more than one hour after detectable levels were no longer present. Since with these doses penicillin is present in measurable amounts in the blood stream for from two to three hours, it can reasonably be assumed that, for all practical purposes, therapeutic activity will cease between the third and fourth hour. These observations are supported by the evidence alluded to previously, indicating that by the end of the fourth hour all but about 5 per cent of the dose administered is excreted in the urine.

A point of interest in this connection is the effect of an increase in the size of the dose upon the duration of therapeutic activity in the blood stream. This is illustrated in Figure 8, in five patients who received single intramuscular injections of 50,000 units, and at a later date additional injections of 100,000 units. Doubling the size of the dose produced blood concentrations twice as high as those observed with 50,000 units, but the duration of assayable blood levels was prolonged by only about one third. This relative inefficiency of larger doses, also pointed out by Fleming,⁴¹ has the additional disadvantage of producing

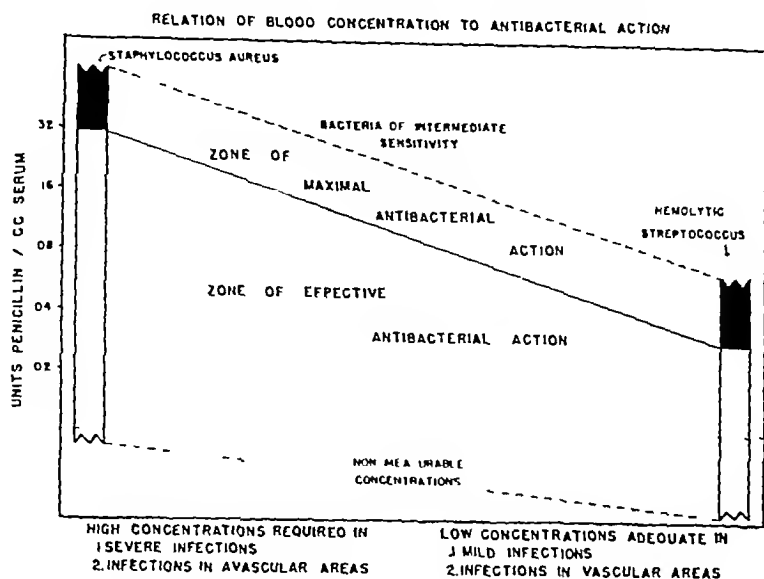


FIG 9

levels in the blood stream which are considerably in excess of those necessary to exert maximal bacteriostasis

The broad relationships of the concentration of penicillin in the blood stream to the sensitivity of various susceptible organisms, as well as to other factors, are summarized diagrammatically in Figure 9. The extremes of variation in susceptibility are represented by the staphylococcus and the hemolytic streptococcus. In addition to the staphylococcus, many strains of *Streptococcus viridans* and non-hemolytic streptococci should be included in the resistant group. Because of the serious nature of infections such as syphilis, diphtheria, and gas gangrene, the organism causing these diseases should also be regarded as highly resistant from a therapeutic standpoint until more information is available concerning their susceptibility both *in vitro* and *in vivo*. Organisms other than the hemolytic streptococcus which may be considered highly sensitive are the gonococcus and pneumococcus. Strains of intermediate sensitivity are represented by the meningococcus. The relative susceptibility of various other organisms, including fungi, spirochetes, and rickettsiae are not definitely known.

Other factors of importance in determining the size of the dose of penicillin are the severity of the infection, the vascularity of the area involved, and the barriers through which penicillin must diffuse or penetrate in order to come into contact with the infecting organisms.

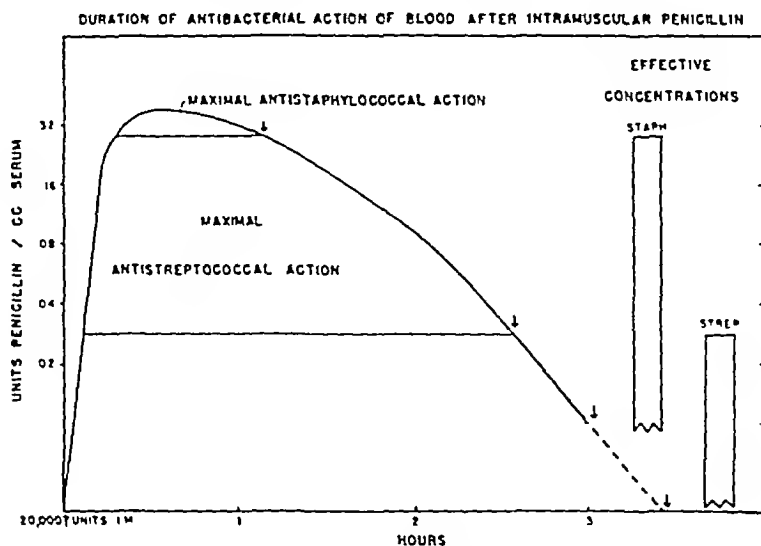


FIG. 10—Arrows indicate time that subsequent injections of penicillin are required to maintain the indicated degree of antibacterial action

The zone of maximal antibacterial action includes concentrations of penicillin which will cause complete inhibition of growth of the bacteria, and which should ideally be maintained throughout the entire period of treatment. However, definite bacteriostasis is exerted by concentrations considerably lower than those regarded as maximal. As indicated on the chart (Figure 9), this zone of effective antibacterial action includes, for highly susceptible organisms, concentrations of penicillin lower than those which are measurable by present methods of assay.

The relationship of these zones of antibacterial activity to blood levels obtained with intramuscular injections of penicillin in saline is presented in Figure 10. An injection of 20,000 units produces levels in the blood stream considered maximal against the staphylococcus for a period of less than one hour, and levels which are definitely bacteriostatic, although not maximal, for another two hours. For the hemolytic streptococcus, on the other hand, the same dose of penicillin produces concentrations having maximal antistreptococcal action for a period of more than two and one-half hours, with partially inhibitory levels for another one and one-half to two hours.

From these figures it is possible to plan rational schemes of therapy for various infections taking into consideration in addition the factors presented in Figure 9. For staphylococcal infections, for example, injections of 25,000 units every two hours will produce optimal continu-

ous levels in the blood stream, for streptococcal infections, 15,000 units every three hours are adequate. It is not within the scope of this paper to make specific recommendations of dosages for various types of infections, the examples cited are presented merely to illustrate the manner in which the dosage schedules are evolved.

The blood concentrations listed in Figures 9 and 10 may also be attained by continuous subcutaneous, intramuscular, or intravenous infusions of penicillin. Although somewhat tedious, these methods of administration are often desirable for the initial treatment of patients seriously ill from overwhelming infections. Blood levels which can be more or less constantly maintained with a continuous intravenous infusion for twenty-four hours are as follows: with 100,000 units, 0.1 unit per cubic centimeter, with 200,000 units, 0.2 unit per cubic centimeter, and with 400,000 units, 0.4 unit per cubic centimeter.²¹ With a continuous intramuscular infusion, the levels are almost identical with those obtained by the intravenous route.³⁴ Subcutaneous administration, however, produces concentrations only about one half as great as those observed with the other two methods.²² Daily dosages adequate for various types of infections may be ascertained by reference to Figure 9.

Two points require special emphasis. One is that doses producing optimal concentrations of penicillin in the blood stream are all that are necessary. Giving larger doses merely raises the concentration of penicillin, without increasing the already maximal antibacterial activity. This point is reiterated with the hope that it will temper the present tendency towards overdosage which, while not harmful to the patient, is wasteful and unnecessary.

The other point is that, for all practical purposes, penicillin remains active in the tissues for only three or four hours following the usual therapeutic doses. Penicillin is often administered only four times a day, leaving a period of twelve hours during which no injections are given. Results obtained with this regimen are so favorable in diseases such as pneumococcal pneumonia²⁸ that there is considerable speculation about the possibility of antibacterial activity remaining in the tissues for many hours after penicillin has apparently left the blood stream. From the data presented in this paper it would appear that this assumption, the implications of which are potentially dangerous, is entirely erroneous.

In conclusion, it must be stated that the exact blood concentrations presented in Figures 9 and 10 cannot be regarded as final from a thera-

peutic standpoint since they are based largely on laboratory observations. Certain factors existing in the tissues, such as the activity of the leukocytes, and the various growth phases of bacteria, are poorly understood, and may eventually alter some of our present concepts. Extensive studies, both clinical and laboratory, will be necessary before a final answer can be reached. For the present, however, the data which are presented are based on sound fundamental observations and provide a basis for the clinical administration of penicillin which is essentially conservative and rational.

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SHOCK THERAPY OF PSYCHOSES EVIDENCES FOR AND AGAINST DAMAGE*

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A VAST literature has accumulated on this subject, which has been studied in all civilized countries of the world. This literature has been reviewed several times by able writers, but it still piles up well in advance of any possibility of dealing with it adequately. However, I shall attempt to present the subject as fairly as possible from several different viewpoints, selecting supportive evidence from a number of available sources.

There are a great many foci of special interest from the viewpoints of the various scientific and clinical disciplines. To mention a few examples, the internist, physiologist and pathologist are interested in studying the bodily organs including the brain (the particular realm of the neuropathologist) during and following the therapeutic procedure, the neurologist and neurophysiologist find their special problems in the behavior of the nervous system under this type of bombardment, the biochemist sees many opportunities to investigate what is taking place in the metabolic processes, the physicist is interested in matters of techniques particularly those involved in electro-physics, and the psychiatrist and psychologist, within whose own territory the whole business is going on, and who must assume the task of evaluating all results in terms of the mental behavior. I nearly omitted the surgeon who has to step in occasionally to patch up the bony structures when the framework yields to the strain.

Although a lot of work has been done, the various reports are difficult of evaluation as there is no uniformity in the diagnosis of mental conditions which in themselves are often not clearly differentiated syndromes, the course and outcome of any patient's case are unpredictable with or without special treatment, and usually controls that are scientifically satisfactory have not been utilized.

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A number of different "shock" therapies have been tried out but the insulin, metrazol and electroshock methods and various modifications of these have dominated the picture. They are the only ones we can undertake to review here, and we shall start with a condensed account of the present concensus on the insulin method.

The indications usually mentioned are the catatonic, paranoid, hebephrenic and simple forms of schizophrenia (these are given in the order of favorable prognosis). Some workers prefer the insulin method to the convulsive ones for other acute and chronic forms of mental disorder. The shorter the duration of the illness the more favorable the prognosis, and those patients who have made a fairly satisfactory life adjustment up to the age of twenty-five or above, and whose disorder is an acute episode, have the best remission rates. Patients under the age of sixteen years show a low remission rate.

In the numerous reports available emphasis has been placed on a number of physical contraindications including coronary disease, severe myocarditis, valvular disorder, cardiac arrhythmia due to organic reasons, tuberculosis, organic impairment of the liver, kidneys or pancreas, and serious endocrine dysfunctions.

A wide variety of complications arising during the treatment itself have been described. Of these may be mentioned particularly auricular fibrillation and gallop rhythm of the heart, myocardial failure, coronary occlusion, aspiration pneumonia, laryngospasm, pulmonary edema, central respiratory failure, asthma, urticaria, aphasia, hemiparesis, and fracture and dislocations of bony structures.

Insulin therapy, according to practically all reports, increases very definitely the percentage of remissions and although many relapses occur, even in these, the patients have a period of better mental health which may allow them to reside outside a hospital. Moreover, it shortens the illness in many of those who might eventually recover spontaneously. The mortality due to the therapy itself, as reported, is less than 1 per cent.

A number of interesting studies have been made of which we have space to mention a few. One of these was made by Bond and Rivers¹ who treated 251 schizophrenics with insulin. This investigation revealed that 138 or 54 per cent were recovered or greatly improved at the end of the treatment, forty-nine of these cases were followed for five years. Of these 22 or 41 per cent had maintained their status. These cases were

compared with 100 control cases, the latter showing only a 16 per cent recovery rate at the end of a five-year period. Bond gained the impression that the quality of the remissions was much superior to that attained in the patients not so treated. There are definite criteria that could be set up to determine this point with certainty. It is possible that with the rather rapid relief from emotional tension experienced by the patient under shock therapy, his compensatory forces are freed more quickly and can work more rapidly towards a reconstruction of the defenses and adjustments than is possible by means of the slower "spontaneous" recovery process.

Gold,² by means of injections of mecholyl chloride, a choline derivative which stimulates the parasympathetic part of the autonomic nervous system rather specifically and by means of which one can unbalance the whole system, was able to study the autonomic balance of schizophrenics before and after insulin shock therapy. Mecholyl chloride produces a temporary lowering of the systolic and diastolic pressures, an increase in pulse rate, flushing of skin, and an increase in salivation, lacrimation and perspiration. In clinically improved patients there was a definitely increased ability on the part of the autonomic nervous system to maintain its balance, and also a more rapid compensatory reaction towards restoration of balance when it was disturbed. The activity of the sympathetic system was improved in particular.

According to Rennie³ the "administration of insulin in subcoma doses provides an effective method of sedation. Its specific action seems to be in alleviation of anxiety. With the relief of anxiety, the psychotic manifestations sometimes rapidly disappear. The method is entirely safe and is far superior to that achieved by chemical sedation." It should be combined with organized psychotherapy.

In inexperienced hands insulin therapy is a risky procedure. Owing to the reports of various types of hemorrhage during treatment, Freed and Wofford⁴ suppose that there is some damage to the walls of the capillaries of the nature of an anoxemia which produces an increased permeability. Such lung complications as bronchopneumonia, lung abscess and pulmonary edema have been reported by a number of writers. Pulmonary edema in the setting of cardiac failure and insufficiency is a symptom that renders the therapist particularly uneasy (O'Neill⁵). Allergic symptoms may appear (Hinko et al⁶) in the form of decrease in tolerance, local reactions, and as an immediate anaphylactic reaction.

indicating appropriate treatment instanter

From the standpoint of the internist, prolonged coma is the most serious of all complications. If the patient does not awaken within thirty minutes after the glucose feeding, the physician should start to do something about it. Instances of prolonged coma have persisted for hours, days or weeks. There may be a high temperature, rapid pulse and respiration, and vomiting and death. Lester⁷ studied twenty-five cases of prolonged coma and reported the mortality rate to be 16 per cent. After considering all reported statistics he thought that a prolonged coma occurs once in every 1,877 treatments.

Different subjects vary a great deal in their susceptibility and response to similar doses of insulin, and also the effects of low blood sugar levels vary widely in different people. These aspects have been discussed by a number of authors. One particularly interesting case was reported by Rivers and Elliott.⁸ This patient "received up to 1200 units of insulin intramuscularly and up to 2500 units intravenously without going into deep stupor. Insulin produced the same total fall in blood sugar" as in those who go into stupor.

The brain is unlike other organs of the body in that it can use only carbohydrate. The brain metabolism is therefore depressed in hypoglycemia. In the convulsive therapies the respiratory movements are interfered with and the brain, as well as other organs of the body, is temporarily deprived of oxygen.

Patients receiving insulin shock therapy reveal a progression of symptoms in a caudal direction. These symptoms seem to present themselves in five groups, each one representing a different phyletic region of the brain, namely cortical, subcortico-diencephalic, mesencephalic, upper medullary and lower medullary. According to the researches of Chesler and Himwich⁹ the order of progression in the depletion of glycogen from the various parts of the dog's brain under the influence of intense hypoglycemia is similar in order of structures, with one exception, in the dog the caudate nucleus is depleted before the cerebral cortex. In these animals the decrease in glycogen concentration "occurred in a definite order which with the exception of the cerebral cortex had a rostral to a caudal progression. The concentrations in the caudate nucleus and in the corpora quadrigemina decreased first, followed by those in the cortex, the thalamus, the cerebellum and the medulla. The values for the cord were never significantly below the normal."

The indications for the application of convulsive therapy (metrazol or electro-shock) are involuntional states, manic depressive psychoses, and other depressive reactions. Convulsive therapy has also been used rather freely and successfully in acute catatonic episodes.

The contraindications are said to be advanced arteriosclerosis and hypertension, auricular fibrillation, cardiac dilatation, recent coronary occlusion, hyperplastic or degenerative skeletal disorders, tuberculosis, seropositive syphilis, and pregnancy. The most frequently seen complications engendered during the treatment are subconjunctival hemorrhages, aspiration pneumonia, pulmonary abscesses, auricular fibrillation, cardiac dilatation, vasomotor collapse, embolic fractures and dislocations of the bony framework, status epilepticus and memory disturbances.

Kolb and Vogel¹⁰ estimated a death rate of 0.05 per cent in 7207 cases treated with electric shock, while Impastato and Almans¹¹ placed it at 0.8 per cent in 11,000 cases.

As far as the mortality rate with the shock therapies is concerned, it is probably considerably higher than has been reported statistically. Deaths due directly or indirectly to these methods must occur here and there all over the country in places where they are not collected into reports and published in the medical journals.

Death is usually due to some other organ than the brain—and in some instances the autopsy fails to reveal the cause of death. Sometimes the cause of death is a hyperpyretic state associated with status epilepticus.

In comparing the two types of convulsive methods it may be said that metrazol is a respiratory stimulant while electro-shock is a respiratory depressant. The memory loss, with electro-shock is greater and more prolonged than with metrazol but electro-shock is easier to administer, less time-consuming, and the convulsions are less severe. Therefore, with metrazol the danger of fractures is greater. The memory and fear of the treatment with metrazol is disturbing to most patients. The "missed" convulsions usually create a great deal of anxiety. With the electro-shock method there are no "missed" convulsions, usually no memory of the treatment, and much less anxiety.

Although the prognosis after metrazol is quite favorable for manic depressive psychoses and rather high for involuntional depressions, the majority of workers consider the prognosis of all these conditions to be somewhat better following electro-shock. Schizophrenics with psycho-

neurotic elaborations have an unfavorable prognosis with all methods of shock therapy

In the application of the electro-shock treatment the effect does not depend upon the strength of the electric current but upon a successful convulsion. As far as the number of electrically induced convulsions is concerned, to produce favorable results, it is recommended that from 8 to 20 treatments usually suffice for depressions except in the paranoid involutional types which may have to be given some additional ones. Manics are given up to 20 treatments with some workers advocating as high as 2 to 3 convulsions per day instead of the usual twice or thrice weekly fits, and schizophrenics often need from 20 to 50 treatments to bring the desired results.

Smith and co-workers¹² in a follow-up study after 2 years experience with electric shock therapy which included 279 patients were impressed with its value in involutional melancholia and manic depressive psychosis. According to this report "manic patients do not hold their recovery as well as those who have an agitated depression. There is no evidence to indicate that electro-shock treatments may prevent future psychotic attacks nor that they might interfere with spontaneous recovery." They were not favorably impressed with the results in schizophrenia and thought this type of therapy of doubtful value in psychoneurotic conditions. Intocostin (Squibb) was used to decrease the incidence of traumatic skeletal injuries.

Combined convulsive therapy and psychotherapy has been advocated by some authors including Moriarty and Weil¹³ but the majority of experienced psychiatrists have not been impressed with the results in the neuroses as far as the shock therapy part of the contribution is concerned. To me the distinction between a psychosis and a psychoneurosis is not a theoretic matter of controversy nor merely an academic exercise. The patterns of the two groups of disorders are different, although it may often require a deep and prolonged study of a given case to reveal the differentiating points as quantitative factors as well as qualitative ones are to be considered.

Favorable results with the electric shock method have been reported extensively and rather consistently, but there are still questions in the minds of some regarding physical complications. Most of the accidents reported are considered to be minor in nature. Some of them can be prevented by the use of curare¹⁴ or by the proper position of the body.

Unless there is a universal tendency to emphasize the favorable results and to minimize the untoward ones, patients are rarely made worse psychiatrically although Kalinowsky and Worthing¹⁵ say that "deeply regressed but quiet patients may become chronically disturbed "

The recovery course is not always smooth. Certain reactions have been pointed out by Osgood¹⁶ as examples. Not infrequently "when the memory clears the depressed mood tends to return, particularly where there are unpleasant situations to be faced, or sometimes the pendulum swings too far and the depressed patient becomes hypomanic, or perhaps the memory does not clear up quickly and the patient fears that the treatment has done him permanent harm "

Some patients do not regain their complete memory after many months. Is it possible that some never attain their original memory-power status?

Osgood¹⁶ in his review of 357 patients treated by electric shock noted panic reactions and perseverative speech in the treatment room and also later reactions such as increased restlessness and agitation, dazed retardation, and states of excitement with uncooperativeness.

It is possible that the "inner life of the person, which may be considered to be the core of the personality, is resistant to the impact involved in shock treatment. The improvements that do take place appear to be limited, so far as is indicated by the results of the Rorschach test, concerned with outer activities, those at the periphery of the personality. Shock therapy is not as effective in reaching the inner personality as either spontaneous remission or deep searching intensive psychotherapy. Schilder made the point that the patient himself is not really reached by shock treatment,"¹⁷ a point which my own experience supports without the slightest doubt. The matrix of the psychosis is not changed, but only the secondary, presenting features. After the most distressing symptoms are removed or modified favorably, the compensatory resources of the patient may aid him in reconstruction. "Clinical changes are associated with greater docility as a result of blunting of the emotional and intellectual life "

Electroencephalographic changes occur during the course of treatment (electric shock) and correlate with amnesia or other evidence of impaired mental function. Where there is no evidence of impaired mental function and no electroencephalographic alteration, clinical improvement does not occur.

If there is little change in the personality except in the intellectual sphere and if the gain which consists of increased intellectual control is at the expense of the total intellectual function or capacity, then perhaps shock treatment effects clinical improvement by impairing the mind of the patient. Is clinical improvement correlated with more or less permanent damage rather than being the result of temporary cerebral anoxia and stimulation of the autonomic mechanisms?

Permanent or temporary alterations in the electroencephalogram following metrazol shock therapy have been reported by Davis and Sulzbach,¹⁸ Finley and Lesko,¹⁹ Polatin and co-workers,²⁰ Levy and associates,²¹ and by Knott and co-workers.²² These authors concur generally that a large number of convulsions will produce electrocortical potentials of high amplitude and low frequency. Knott and his associates²³ in studying electroencephalographically twenty depressed patients given metrazol shock therapy observed "(1) no significant group variation in alpha index following metrazol shock therapy although there were striking individual changes, (2) there was significant variation in slow activity after such therapy, (3) this variation was made manifest as an increase in activity of less than 6 per second frequency in the motor and frontal areas, (4) there was evidence that the amount of slow activity following therapy was conditioned by the amount of such activity preceding therapy, (5) there was individual susceptibility to change in slow wave activity."

These same workers studied also the changes in the electroencephalogram following insulin shock treatment and found an increase in the alpha index in 8 of the 10 schizophrenic patients studied. This was more prominent in the frontal areas. There were no notable uniform durations in slow activity.

In an experiment by Stanbrook²⁴ a group of 28 rats learned a maze under the usual hunger motivation. Then some of them were given one electro-shock daily for thirty days. When all the animals were tested in the maze twenty days after the shock routine had been terminated, both the relearning time and the relearning error scores were definitely greater than the corresponding scores of the control animals. It is perhaps significant that the re-learning error scores of the experimental animals were about the same as they were in the initial learning experience. This author pointed out the possibility that the errors in re-learning might be due to some emotional conditioning induced by shock experience,

and that this should be considered before concluding that there had occurred an "enduring disorganization of the purely discriminative cognitive structural-trace of a recent maze habit" It is possible, if not probable, that this phenomenon in the rat corresponds to the memory difficulties noted in patients during and following the therapy

Although subconvulsive shock therapy has been advocated by some workers it was found to be practically valueless by Gottesfeld and his associates²⁵ In their series of twenty-four cases of affective psychosis none were improved and many of them showed fear and apprehension as a result of their experiences under the subconvulsive technique No case of schizophrenia showed any improvement However, Plattner and Lohns²⁶ reported good results in a number of depressions particularly in those of the senile and arteriosclerotic group where the weaker currents were tolerated better by these aged and fragile persons

The problem of circulatory failure has been presented by a number of writers Jetter²⁷ concluded that there were at least two mechanisms to consider by which fatal circulatory failure could occur, i e, an acute cardiac dilatation brought about by the muscular exertion of the convulsion, or by means of the electrical stimulation of hyperexcitable central cardiac or vasomotor centers He reported the deaths of three patients from circulatory failure Of these two had advanced arteriosclerotic cardiac disease and the other an acute myocardial condition These are mentioned here to emphasize that there are hazards of this character in this field that one should take fully into consideration during the selection of patients

A number of histopathological researches have been carried out on brain tissue Lidbeck²⁸ concluded from his studies on the dog that therapeutic electric shock is not contraindicated in the therapy of psychoses No correlation was found between the amount of current used and the brain changes which were minimal

Horses and dogs are killed with relatively small charges of electricity as contrasted with rabbits and rats which are rather resistant [Jaffé²⁹], and human beings vary a great deal in their sensitivity to electric currents

The earlier experiments on animals were with lethal or sublethal or maximum charges and therefore the resulting brain changes should have been expected³⁰ Even then they have not been too startling although they were the result of "acute experiments" Gross petechial hemor-

rhages of the meninges, capillary injection, microscopic hemorrhages, with swelling and demyelination of the axis cylinders, gliosis, degeneration of nerve cells, vacuolization of oligodendroglia and white matter have all been described in experimental animals

In a very painstaking neuropathological research on cats to determine the significance of the intracerebral vascular reaction Alexander and Lowenbach³¹ discovered a number of interesting things which we cannot spare the time to discuss here, but among their conclusions one finds the following pertinent statement "With single shock doses within the range of amperage used in electro-shock treatment in man, no pathological changes of the neural parenchyma could be produced which were recognizable with present-day histological methods at times varying from 4 minutes to seven days after the shock. It is concluded that early organic physiological and physico-chemical changes of the neural parenchyma must nevertheless exist, but that they are of an order not yet demonstrable morphologically. The nature of these early physiological and physico-chemical changes awaits future investigation. The question of late changes is likewise uninvestigated and open to future study."

Practically the same conclusions were reached by Winkelman and Moore³² who also utilized cats in the experiments. Their careful histologic studies of the brains and cords failed to show any morphologic changes in the animals receiving convulsive doses analogous to those given to humans. Excessive doses do have some tendency to produce congestion and small hemorrhages. Winkelman and Moore suggest that in many experiments reported (1) the intensity of the current which produces lesions in experimental animals may be excessive as compared with that used in human therapy, and (2) the animals may have metabolic, nutritional, disturbances or lack of certain vitamins such as B, C, or K during the course of the experiments.

Heilbrunn³³ concluded from his rat experiments that the electric current as such was not responsible for the hemorrhages in the nervous system which resembled those described previously by Alpers and Hughes³⁴ and by Heilbrunn and Weil³⁵ since such demonstrable lesions occurred in the animals in which ether had been used to prevent the convulsion. This investigator was inclined, therefore, to attribute the occurrence of hemorrhages to changes in dynamic pressure associated with the muscular contractions and their attendant blood vessel changes.

Preparatory treatments with atropine, calcium, vitamin K, and a suspension of brain substance were ineffective as protection against the pressure reactions

Hemorrhages were found in the pia arachnoid and also in the brain substance. Those in the meninges were most frequent over the base of the brain where congestion of the vessels was also prominent. Hemorrhages into the brain substance were noted through the cortex of the hemispheres, in the hypothalamic area, in the cerebellum, and particularly in the medulla and pons. With few exceptions they were petechial in type, and as they were found to be in different stages of progressive organization this indicated that some of them had occurred at the beginning during the early treatments. The group of animals having the true convulsive seizures, rather than mild attacks, revealed the most extensive and numerous hemorrhages.

It has been demonstrated that the cellular constituents of the blood are increased after convulsive treatment and chemical studies have shown that amino acids, cholesterol, vitamin C, reducing substances, oxygen, total phosphorus (organic phosphorus, acid soluble phosphorus, inorganic phosphorus), chlorids, sodium, potassium, calcium and magnesium as well as the icteric index were altered in amounts after treatment. Increases were more frequent than decreases excepting the amino acids which were decreased more than twice as frequently as increased (Katzenelbogen). Carbon dioxide was decreased after nearly all treatments, Katzenelbogen³⁰ suggests that this would seem to indicate hyperoxemia rather than anoxemia which has been stressed by several writers.

Since many of these constituents return to normal or become subnormal after a few hours the changes may be due to dehydration. Fluids leave the blood stream while the less diffusible substances remain. There is an increased mobility and acidity of the stomach.

CONCLUSIONS

Taking everything into consideration and after analyzing the mass of literature that has accumulated on the shock therapies, one is convinced that they have a definite place in the practice of psychiatry when they are applied by the properly qualified physician possessing the clinical sense, experience and judgment necessary to manage a psychiatric problem. Owing to unexpected complications which may develop at any time patients should always be treated in a hospital setting or at home.

with the proper medical and nursing facilities. They should not be treated in the offices of physicians nor in outpatient clinics to be turned loose on the street following the therapy. The greatest advantage of the insulin method seems to be in its effect on schizophrenia, while the convulsive therapy methods are found to be the applications of choice in the affective conditions in whatever setting they have developed.

At the Psychiatric Institute monkeys subjected to electric convulsions similar to those given to humans therapeutically were studied for brain lesions. The few changes noted were found in the brains of the control animals. Therefore whatever their source might have been it was not the result of shock therapy.

Most of the vertebral fractures noted are of very little clinical importance, but are chiefly of roentgenographic significance—frequently rather indistinct in nature.

The evidence all the way through this multiphasic problem indicates clearly that the reported therapeutic results are influenced by the subjective bias or attitude of the investigator, by the adequacy of the shock therapy itself, and by the possible effect of such adjuvant measures as psychotherapy, physiotherapy, etc. Moreover, the degrees of "remission" remain to be defined in a way acceptable and utilizable by the workers. Until these factors are recognized and adjusted universally the total situation will remain difficult to evaluate.

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